Towards ending tuberculosis in a high burden multidrug-resistance setting: strategies for prevention

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Abstract

Multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) represents a major challenge to achieving the World Health Organisation's (WHO) target to end tuberculosis (TB) by 2035. Traditional responses have focused primarily on detection and treatment, with an emerging but limited role for TB preventive treatment (TPT), which involves treating TB infection. This thesis addresses the critical need for prevention strategies in high-burden MDR/RR-TB settings through research conducted in Papua New Guinea (PNG).

This collaborative program of operational and implementation research was conducted and embedded within the programmatic TB response from 2014 to 2022, evaluating interventions to detect, treat, and prevent TB, including MDR/RR-TB in South Fly District, one of the highest TB burden settings globally. A literature review established the evidence base for comprehensive public health strategies to end TB, focussing on the role of screening, contact investigation and TPT.

The first study was a retrospective cohort analysis evaluating TB detection and treatment outcomes and factors associated with unfavourable outcomes from 2014 to 2022. It demonstrated that while dramatic improvements in treatment success rates are achievable in fragile health system settings, detection and treatment alone were insufficient to reduce TB incidence.

The second study employed qualitative methods to examine the socio-ecological determinants and treatment experiences of people with TB in South Fly District. This revealed how person-centred community-based care models improved patient experiences, while identifying the severe structural barriers to accessing and utilising TB care and unique socio-cultural family and household dynamics that informed the model of care.

The third study was a prospective implementation study that demonstrated the feasibility of community-based TB contact investigation with newer TPT regimens for young child (<5 years) contacts of people with TB, including MDR/RR-TB. Findings showed that exposure and transmission were occurring outside households, highlighting the limitations of household-based prevention strategies in this context.

These studies collectively informed the development of SWEEP-TB, an innovative, comprehensive community-wide intervention protocol that combines screening and detection of active TB with testing and treatment of TB infection, using a novel TPT regimen with activity against MDR/RR-TB.

This thesis supports the argument that, to reduce TB incidence in high-burden settings, prevention strategies focused on TPT need to be extended beyond household and close contacts to the wider community, as part of a comprehensive approach. The findings provide critical evidence for operationalising the WHO End TB Strategy in low- and middle-income settings, with broader applicability to similar remote settings globally. The studies have directly informed TB policy and program planning in PNG and contribute to global evidence informing the implementation of comprehensive TB prevention strategies.

Declaration

This is to certify that:

i. This thesis comprises only my original work except where indicated in the preface,
ii. Due acknowledgement has been made in the text to all other material used
iii. The thesis is fewer than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices

Suman Majumdar

Date: 28th August 2025

Preface & statement of contribution

This thesis represents my original work conducted as part of a larger collaborative program of clinical, public health and research to respond to tuberculosis and strengthen the health system in Western Province, Papua New Guinea (PNG). Burnet Institute's Reducing the Impact of Drug-resistant TB (RID-TB) project works in partnership with the Western Provincial Health Authority (WPHA), PNG National Department of Health and implementation and research partners, supported by the Australian Government.

As technical director of RID-TB from 2014-2021, I led a large multidisciplinary team consisting of doctors, nurses, public health specialists, community health workers, community engagement staff, research and data management staff and project administration staff based in PNG and Australia. In this role, I was instrumental in designing and implementing the programmatic interventions described in this thesis, as well as conducting significant foundational work prior to my PhD enrolment in 2019. This included, working in partnership with the WPHA to develop the programmatic TB strategy, establishing clinical, public health and data systems, and implementing the emergency response to TB in South Fly District and initiating subsequent operational and implementation research, including a capacity building program (SORT-IT).

All chapters represent original work conducted specifically for this thesis and there are no incorporated publications. Three related publications where I was senior or first author are included in the Appendix as some content draws upon these publications. For two publications related to Chapter 3 (Morris et al., 2019; Bauri et al., 2024), I was responsible for conceptualisation, protocol development, analysis plan development and writing initial and final drafts as lead facilitator during operational research training (SORT-IT) with the TB program leaders from the WPHA. The two datasets from these studies were combined into a single cohort and I undertook additional analyses, as well as a comprehensive description of programmatic activities, making it original work. For the publication related to Chapter 6 (Majumdar et al., 2023), I was first and corresponding author, responsible for conceptualisation, study design, protocol development, data analysis, and manuscript preparation.

None of the work contained in this thesis has been submitted for other qualifications. All chapters are entirely my work and have been supervised by Professor Steve Graham and co-supervised by Professor Leanne Robinson, with Professor Phillip Hill, and Professor Greg Fox as external supervisors. The bibliography of this thesis was edited by Elite Editing, and editorial intervention was restricted to Standards D and E of

the Australian Standards for Editing Practice. Additional third-party human or digital editorial assistance was not used in the preparation of this thesis, other than that stated below.

My primary supervisor, Professor Steve Graham provided technical and strategic advice on clinical and public health implementation prior to and throughout the undertaking of this PhD, support for the partnership with stakeholder engagement and through operational research training guidance for the research activity and procurement of research grant funding. As a large collaborative program, public health and research implementation staff were employed under my supervision for the work described in Chapters 3, 4, 5 and 6. Importantly, this included locally engaged research assistants for data collection and management.

The following third-party assistance was provided: I designed the protocol and analysis plan for Chapter 3 and Dr. Stef Vaccher (knowledgeable in epidemiology and biostatistics) provided advice on statistical coding and analysis that I conducted for Chapter 3. I designed the protocol and analysis plan for Chapter 4 and Dr Paul Mason, Dr Angela Kelly-Hanku and Ms Agnes Mek (knowledgeable in qualitative research methods) advised on protocol development, provided local supervision of qualitative research implementation and training of research assistants for Chapter 4. A/Prof. Steve Bell (knowledgeable in qualitative research methods) advised on the qualitative research methodology and analysis that I conducted for Chapter 4. I designed the protocol and analysis plan for Chapter 5 and Mr Geoff Chan (knowledgeable in biostatistics and managed the programmatic and research data systems) provided technical support for statistical coding and analysis. For the full thesis chapters, I guided the analysis, interpreted all results, and wrote all chapters.

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The programmatic and research implementation in PNG was supported by Australian Government funding through multiple grants, which I obtained and/or contributed to, either as the primary investigator or a co-investigator:

- RID-TB project (DFAT, 2015-2025)
- NHMRC TB-CRE seed funding: Characteristics and health narratives of people in households exposed to DR-TB on Daru, PNG (GNT1043225), 2018-19
- TDRRCI HOT-NORTH pilot project: Enhanced screening and preventive therapy for TB in Daru, PNG (GNT1131932), 2019-22
- TDRRCI: Strengthening Regional Research Collaboration in the Prevention and Containment of MDR-TB and Malaria (GNT1132089), 2016-2018
- DFAT NHMRC International Joint Calls: Stronger systems for drug-resistant TB and Malaria (GNT1152867), 2018-21
- MRFF Global Health: Comprehensive Community-based solutions to reduce MDR-TB in high burden settings (MRF1201008), 2020-25

The funders had no role in study design, data collection, analysis, interpretation, or writing.

Publications arising from this thesis

Chapter 3:

Morris L, Hiasihri S, Chan G, Honjepari A, Tugo O, Taune M, Aia P, Dakulala P, **Majumdar SS** The Emergency Response to Multidrug-resistant Tuberculosis in Daru, Western Province, Papua New Guinea, 2014-2017. *Public Health Action*. 2019 Sep; 9(Supplement 1):S4-S11.

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Chapter 7:

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This thesis emerges from both profound challenges and inspiring solutions in addressing one of humanity's oldest diseases. The tuberculosis (TB) crisis in South Fly District, PNG, exemplifies the moral, scientific, and political failures that perpetuate health inequities globally. The individual and collective suffering I witnessed, the fragility of health systems, and the neglect of communities like Daru, reflect broader patterns of privilege and power that have allowed TB to persist as a disease of poverty and disadvantage. This work was conducted with deep awareness of colonial legacies—both Australia's colonial administration of PNG and my own family's experience under British colonial rule. These histories have shaped health inequities and my understanding of the need for fundamentally different approaches to partnership.

Yet, this work also demonstrated to me the exceptional local leadership in PNG and genuine partnership that can be established in the context of international assistance and research models that inherently carry power imbalances. My partnership with Dr. Stenard Hiasihri exemplified what authentic collaboration can achieve—a relationship built on mutual respect, shared learning, and service to community rather than extraction of knowledge. This partnership included exceptional and inspiring PNG leaders who worked hard to serve their communities - Ms. Alice Honjepari, Ms. Lucy Morris, Dr. Maggie Taune, Sr. Orpah Tugo, Dr. Niko Wuatai, Dr. Mathias Bauri in Daru and Dr. Paul Aia, Dr. Margaret Kal, and Prof. Willie Pomat at the national level. I pay special tribute to the late Dr. Paison Dakulala, a visionary PNG leader whose commitment to TB health equity was unwavering, and the late Prof. Evelyn Lavu, who was a trailblazer in clinical and public health service. We lost them both too early. I learned so much from them. Their contribution to improving the health of PNG was unparalleled. I acknowledge the, now over a hundred, TB program staff and leaders – from PNG, Australia and around the world - who worked in the TB program for their immense service and contribution. I thank this large team, including but not limited to Khai Huang, Geoff Chan, Tope Adepoyibi, James Lawson, Peter Wallis, Lucia Gonzalez, Pilar Ustero, Kudakwashe Chani, Tess Keam, Allan Kuma, Shahid Islam, Stacia Finch, Abby Peacock Smith, Camila Burkot, Homini Doroguri, Darius Arona, Miriam Ase, Ethel Pamumum, Bisato Gula and Kyrol Kaison.

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My PhD was not without significant challenges. The COVID-19 pandemic hit in year one of my studies, and I took on a leadership role in Australia's pandemic response, including serving as Deputy Chief Health Officer. Additionally, I took parental leave for the birth of my two children, resulting in 18 months of leave from PhD studies. Words cannot convey my gratitude to my partner, Elly, who provided clarity, pragmatic guidance, and unwavering support. While we both shared caring responsibilities, she carried the majority, enabling me to complete this work. Our children Arlo, Esme, and Nina have been my greatest motivation. I thank the many people who provided care for them, making this work possible, especially Amelie, Christina and Nadine. This work would not have been possible without Pauline, who has been an extraordinary source of strength, practical assistance, and wisdom, helping us navigate the demands of care and work. I thank those who provided support, pragmatic advice and encouragement - Avik, Josh, Margaret, Kara and many friends. I acknowledge the profound position of privilege I have, in undertaking this work and doctoral studies. I am deeply grateful to my parents, whose journey as migrants to Australia involved sacrifice and determination to create opportunities. Their resilience, values, and commitment to education have profoundly

shaped my path and my understanding of the responsibility that comes with such privilege.

The work in this thesis reinforces that TB persists not because we lack scientific solutions, but because of scientific and moral failures in applying what we know. As demonstrated in Daru, TB continues to devastate communities despite being entirely curable and having robust prevention strategies. The science exists; what we need is the moral courage to apply it equitably, the political will to address root causes, and the humility to centre affected communities in both research and solutions. This thesis represents a true collaboration between researchers, clinicians, communities, and governments working together toward the shared goal of ending tuberculosis. The people of Papua New Guinea and the Daru community have taught me that addressing complex challenges requires not just scientific rigour, but humility, partnership, and addressing the systems that perpetuate injustice. The partnerships forged and the local leadership developed through this work provide hope for sustained progress and represent one small contribution to the larger struggle to end TB and towards health equity.

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List of Abbreviations

3HR	3 months isoniazid and rifampicin
6H	6 months isoniazid
6HLfx	6 months isoniazid and levofloxacin
6Lfx	6 months levofloxacin
ACF	Active case-finding for tuberculosis
AIDS	acquired immune deficiency syndrome
ART	antiretroviral therapy
BCG	bacille Calmette-Guérin
C-DST	culture and drug susceptibility testing
CAD4TB	computer-aided detection for tuberculosis
CI	confidence interval
CNR	case notification rate
COVID-19	coronavirus disease due to SARS-CoV-2
CSIRO	Commonwealth Scientific and Industrial Research Organisation, Australia
CXR	chest radiography
DPH	Daru Provincial Hospital
DR-TB	drug-resistant tuberculosis
DS-TB	drug-susceptible tuberculosis
DST	drug susceptibility testing
EMRS	electronic medical record system
HEO	health extension officer
HICs	high-income countries
HIV	human immunodeficiency virus
IGRA	interferon-gamma release assay
Lfx	levofloxacin
LMICs	low- and middle-income countries
LTFU	loss to follow-up
MDR-TB	multidrug-resistant tuberculosis
mWRD	WHO-recommended molecular rapid diagnostic test
NCD	National Capital District
NDoH	National Department of Health, Papua New Guinea
NHMRC	National Health and Medical Research Council, Australia
NTP	National Tuberculosis Program
PICs	Pacific Island countries
PLHIV	people living with HIV
PNG	Papua New Guinea
RR-TB	rifampicin-resistant tuberculosis
SFD	South Fly District

SOP	standard operating procedures
SORT-IT	Structured Operational Research Training Initiative
SWEEP-TB	Systematic Community-Wide Engagement & Elimination Project for TB
TB	tuberculosis
TBI	tuberculosis infection
TPT	tuberculosis preventive treatment
TST	tuberculin skin test
UI	uncertainty interval
WHO	World Health Organisation
WPHA	Western Provincial Health Authority
WRD	WHO-recommended rapid diagnostic test
XDR-TB	extensively drug-resistant tuberculosis

Definitions

Unless otherwise specified, all definitions follow current World Health Organisation consolidated guidelines and recommendations for tuberculosis (2020-2025).

Clinical and programmatic definitions

***Mycobacterium tuberculosis* (*M. tb*):** a species complex comprising closely related organisms that primarily cause TB in humans (*M. tuberculosis*, *M. africanum*, *M. canetti*), primarily cause disease in animals but can infect humans (*M. bovis, M. caprae, M. pinnipedii)* and primarily cause animal disease *(M. microti, M. mungi, M. orygis, M. suricattae*). This thesis focuses on the primary human pathogen, *M. tuberculosis*, that causes the vast majority of human TB.

Tuberculosis (TB): the disease that occurs in someone infected with the *M. tuberculosis* complex. It is characterised by signs or symptoms of TB disease and may occur without symptoms. Referred to as “active” TB or TB “disease” to distinguish it from TB infection

TB infection (TBI) or latent tuberculosis infection: a state of persistent immune response to stimulation by *M. tb* antigens with no evidence of TB disease (active TB). TBI is determined by evidence of an antigen-specific T cell response to mycobacterial proteins measured by reactivity in the tuberculin skin test (TST, also known as a Mantoux test) or an interferon-gamma release assay (IGRA). There is no test for direct identification of *M. tb* infection in humans.

TB preventive treatment (TPT): treatment offered to individuals who are considered at risk of progression from TB infection to TB disease. Also referred to as treatment of TB infection, treatment for latent TB infection or TB preventive therapy.

WHO-recommended rapid diagnostic test (WRD): a test approved by WHO that employs molecular (e.g. Xpert Ultra) or biomarker-based techniques (e.g. urinary lipoarabinomannan assays (U-LAM)) for the diagnosis of TB. Often the term molecular WRD (mWRD) is used.

Bacteriologically confirmed TB: a person from whom a biological specimen is positive by a WHO-recommended rapid diagnostic test, culture or smear microscopy. Also called microbiologically confirmed TB.

Clinically diagnosed TB: a person who is diagnosed with TB but is not bacteriologically confirmed.

Asymptomatic TB: a person with TB disease who did not report symptoms suggestive of TB during screening. Also called sub-clinical TB or incipient TB.

Child: a person under 10 years of age (WHO), however in TB reporting and surveillance for WHO is a person under 15 years of age.

Infant: a child under 12 months of age

Adolescent: a person aged 10–19 years

Adult: a person over 19 years of age

Drug susceptibility testing (DST): in vitro testing of a strain of *M. tb* complex using either: 1) molecular, genotypic techniques to detect resistance-conferring mutations; or 2) phenotypic methods to determine susceptibility to a medicine.

Drug-resistant TB (DR-TB): A person with TB disease who is infected with a strain of *M. tb* complex that is resistant to any TB medicines tested. When available, DST results for individual drugs should be recorded.

Drug-susceptible TB (DS-TB): a person with TB disease for whom there is no evidence of infection with a strain of *M. tb* complex that is resistant to rifampicin or isoniazid. This includes people for whom DST was not done or for whom DST shows a strain that is susceptible to both rifampicin and isoniazid.

Isoniazid-resistant, rifampicin-susceptible TB (Hr-TB): a person with TB disease who is infected with a strain of *M. tb* complex that is resistant to isoniazid but susceptible to rifampicin.

Rifampicin-resistant TB (RR-TB): a person with TB disease who is infected with a strain of *M. tb* complex that is resistant to rifampicin. Note: These strains may be either susceptible or resistant to isoniazid (i.e. MDR-TB) or resistant to other first-line or second-line TB medicines.

Multidrug-resistant TB (MDR-TB): a person with TB disease who is infected with a strain of *M. tb* complex that is resistant to both rifampicin and isoniazid. MDR-TB is a subset of RR-TB, and the two are often grouped together using the term MDR/RR-TB.

Pre-extensively drug-resistant TB (pre-XDR-TB): a person with TB disease who is infected with a strain of *M. tb* complex that is resistant to rifampicin (and which may also

be resistant to isoniazid), and which is also resistant to at least one fluoroquinolone (either levofloxacin or moxifloxacin).

Extensively drug-resistant TB (XDR-TB): a person with TB disease who is infected with a strain of *M. tb* complex that is resistant to rifampicin (and which may also be resistant to isoniazid) as well as resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and at least one other 'Group A' drug (bedaquiline or linezolid).

Systematic screening for TB disease: systematic identification of people with presumed TB disease, in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly. Among those screened positive, the diagnosis needs to be established by one or several diagnostic tests and additional clinical assessments, which together have high accuracy.

Active case-finding (ACF): synonymous with systematic screening for TB disease, although it normally implies screening that is implemented outside of health facilities

Index case (index patient) of TB: the initially identified person of any age with new or recurrent TB in a specific household or other comparable setting in which others may have been exposed. An index case is the person on whom a contact investigation is centred but is not necessarily the source case

Contact investigation: a systematic process for identifying previously undiagnosed people with TB disease and TB infection among the contacts of an index TB patient and/or other comparable settings where transmission occurs. Contact investigation consists of identification, clinical evaluation and/or testing and provision of appropriate anti-TB therapy (for confirmed TB cases) or TB preventive treatment (for those without TB disease). Also known as contact screening and management.

Contact: any individual who was exposed to a person with TB disease.

Close contact: a person who is not in the household but shared an enclosed space, such as at a social gathering, workplace or facility, for extended periods during the day with the index case during the three months before commencement of the current TB treatment episode.

Household contact: a person who shared the same enclosed living space as the index case for one or more nights or for frequent or extended daytime periods during the three months before the start of current treatment.

Measures of TB Burden

TB incidence: the number of new and recurrent (relapse) episodes of TB (all forms) occurring in a given year, expressed as the rate per 100,000 population.

- Direct measures of national incidence through population-based surveys are not feasible to conduct.
- Case notifications of TB cases provide a good proxy indication of TB incidence in countries that have both high-performance surveillance systems (where there is little under-reporting of diagnosed cases) and where the quality of and access to health care means that few cases remain undiagnosed and overdiagnosis is limited.
- In the majority of countries, these criteria are not met and therefore estimates are used. The WHO measurement method for incidence is detailed in the 2024 Global TB Report[1] and is based on one of five methods that use prevlance surveys, inventory studies, modelling, notification data and expert opinon.

TB prevalence: the number of cases of tuberculosis (all forms) in a population at a given point in time (usually the middle of the calendar year), expressed as the rate per 100,000 population.

High TB transmission setting: a setting with a high frequency of individuals with undetected or undiagnosed TB disease, or where infectious TB patients are present and there is a high risk of TB transmission.

- High TB burden settings: Countries or distinct parts of countries characterised by a high burden of TB (TB incidence >100/100,000 population)
- Low TB burden settings: Countries or distinct parts of countries characterised by a low burden of TB (TB incidence <10/100,000 population).

High burden countries[2]: countries with the highest absolute number of estimated incident cases, and those with the most severe burden in terms of incidence rates per capita. WHO has defined three lists: one for TB, one for MDR-TB and one for TB/HIV.

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[1] World Health Organisation. Technical Appendix. Global Tuberculosis Report 2024. Geneva: World Health Organisation; 2024. Available from: https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/tb-reports/global-tuberculosis-report-2024

[2] World Health Organisation. Use of high burden country lists for TB by WHO in the post-2015 era. Geneva: World Health Organisation; 2015. Available from: https://iris.who.int/handle/10665/341980

- High TB burden countries: The 20 countries with the highest estimated numbers of incident TB cases, plus the 10 countries with the highest estimated TB incidence that are not in the top 20 by absolute number (threshold: >10 000 estimated incident TB cases per year).
- High MDR/RR-TB burden countries: The 20 countries with the highest estimated numbers of incident MDR/RR-TB cases, plus the 10 countries with the highest estimated MDR/RR-TB incidence that are not in the top 20 by absolute number (threshold: >1000 estimated incident MDR/RR-TB cases per year).
- High TB/HIV burden countries The 20 countries with the highest estimated numbers of incident TB/HIV cases, plus the 10 countries with the highest estimated TB/HIV incidence that are not in the top 20 by absolute number (threshold: >10 000 estimated incident TB/HIV cases per year).

- High-income countries[3]: Defined by the World Bank as countries with a gross national income (GNI) per capita of US$ 12 236 or more in 2016, calculated using the Atlas method.

- Low- and middle-income countries[3]: Defined by the World Bank as countries with a GNI per capita, calculated using the World Bank Atlas method, of US$ 12 235 in 2016. This group includes low-income countries (GNI per capita <US$ 1005); lower middle-income countries (GNI per capita of between US$ 1006 and US$ 3955) and upper middle-income countries (GNI per capita of between US$ 3956 and US$ 12 235).

[3] World Bank. World Bank Country and Lending Groups. Washington, DC: World Bank; 2017. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519

Chapter 1: Introduction

1.1 Background and key definitions

Tuberculosis (TB) is an airborne infectious disease and remains a major global public health issue.[1] TB was first described over 3,000 years ago and, the causative agent, *Mycobacterium tuberculosis* was only identified in 1882.[2] Despite significant advances in diagnosis and treatment over the past century, TB continues to exact an enormous toll on global health, making it a leading cause of death from an infectious disease and claiming more lives than HIV/AIDS and malaria combined.[1]

The burden of TB reflects profound health and socio-economic inequities. TB was initially a global problem, but it was virtually eliminated in high income countries (HICs) in the 1950s to 1970s through effective disease control programs and rapid improvements in the social determinants of health. Currently, 99% of the TB burden is found in lower- and middle-income countries (LMICs) and within all countries, TB affects people and communities who are most disadvantaged.[1] This stark disparity underscores TB's role as both a disease of poverty and a driver of poverty, perpetuating cycles of disadvantage in the communities it affects.[3] TB has been considered a global public health emergency since 1993 and concerted responses and resource mobilisation have saved millions of lives.[4] Despite this, the persistence of TB as a major killer in the 21st century represents a profound failure to translate scientific advances into global health equity.[5–8]

TB transmission and disease states

Disease due to *Mycobacterium tuberculosis (M. tb)* is often referred to as 'active' TB to distinguish it from TB infection (TBI).[9] Transmission occurs when *M. tuberculosis* is expelled from the respiratory tract of a person with TB disease and transmitted in small particles through the air, where it is inhaled into the respiratory tract of the next host.[10,11] The bacteria encounter the immune system, where they may be cleared or cause infection, which in turn may progress to disease. TB disease may occur in the lungs (pulmonary TB), and/or spread outside the lungs to other organ systems (extrapulmonary TB). Pulmonary TB classically presents as a subacute illness with fever, weight loss and chronic cough; however, disease may occur with or without symptoms. Subclinical or asymptomatic TB is increasingly being recognised as an important (active) disease state and contributor to TB transmission.[12,13]

TBI or latent tuberculosis infection, is a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of TB disease (active TB). There is no test for the direct identification of *M. tuberculosis* infection in humans, including the resistance profile of the infecting strain. Evidence of an antigen-specific T cell response to mycobacterial proteins measured by reactivity in the tuberculin skin test (TST, also known as a Mantoux test) or an interferon-gamma release assay (IGRA), a blood test. Approximately one-quarter of the global population is estimated to have been infected with TB.[14] Following infection, the risk of developing TB disease is highest in the first two years (approximately 5-10%), after which it is much lower.[15–17] The risk of developing TB disease following infection varies significantly based on age, immune status, and various medical and social risk factors, which contribute to the unequal global distribution of TB burden.

Drug-resistance definitions

Multidrug-resistant tuberculosis (MDR-TB, resistance to at least isoniazid and rifampicin; MDR/RR-TB the two most effective first-line TB drugs) is a major threat to achieving the World Health Organisation's (WHO) target to end the TB epidemic by 2035.[1,18,19] Surveillance and reporting of MDR-TB, includes rifampicin-resistant TB (abbreviated as MDR/RR-TB), as this strain requires the same treatment regimen as MDR-TB. WHO uses five categories to classify cases of drug-resistant (DR) TB (see Key Definitions): isoniazid-resistant, rifampicin susceptible TB (Hr-TB); rifampicin-resistant TB (RR-TB); MDR-TB; extensively drug-resistant TB (XDR-TB); and pre-XDR-TB. Pre-XDR-TB is TB that is resistant to rifampicin and any fluoroquinolone. XDR-TB is TB that is resistant to rifampicin, plus any fluoroquinolone, plus at least one of bedaquiline or linezolid (key drugs for MDR-TB).

Epidemiological definitions

The WHO definitions from the most recent guidelines and documents are used in this thesis, unless otherwise specified. Detailed definitions are provided in Key Definitions. As global TB policy underwent a paradigm shift with the WHO's End TB Strategy (2015-2035), so did the language and terminology.[20,21] It was recognised that paternalistic and stigmatising language was often used, for example, 'defaulter, suspect, case, control.'[22] As a result of work by civil society and researchers, the Stop TB Partnership has developed guidance on person-centred language, aligned with a human rights-based approach to TB care and prevention, that will also be adopted in this thesis.[23]

Tuberculosis burden is quantified using various epidemiological measures and frameworks. Key measures of disease activity, which are usually expressed as a rate per 100,000 population, include incidence (the number of new episodes of TB occurring in a population over a year), case notification rates (the number of cases reported to surveillance systems), and prevalence (the total number of cases existing at a point in time). Measures of impact focus on mortality rates but also include catastrophic costs from TB and disability-adjusted life years. Most importantly, TB incidence can refer to either case notification rates derived from surveillance data, or modelled estimates that account for under-detection and under-reporting. The WHO provides both surveillance-based notifications and modelled incidence estimates for each country in the annual Global TB Report, with detailed methods outlined in the technical appendices.[1,24]

In 2021, WHO defined high TB burden countries using three categories based on absolute numbers or incidence rates: high TB, high TB/HIV and high MDR-TB burden countries. These classifications guide global resource allocation and technical assistance priorities.[25] More recently, for the sub-national application, WHO has defined high TB burden settings as TB incidence >100 per 100,000 and low as <10 and a high TB transmission setting where there is a high frequency of undetected cases or infectious TB.[26]

The global strategy for TB has moved from control to an ambitious goal of elimination. Ending TB refers to the WHO's End TB Strategy goals of achieving a 90% reduction in TB incidence (along with a 95% reduction in TB deaths and no catastrophic costs) by 2035, compared with 2015 levels.[27] TB elimination targets have been defined for low-incidence countries, as <10 cases per million population and elimination as <1 case per million population and frameworks have been proposed on more actionable steps.[28–30]

1.1.1 The global epidemiology of TB and drug-resistance

TB has a long history of co-evolution, adaptation and transmission between humans and is estimated to have emerged 70,000 years ago.[31] The disease was the leading cause of death in the 18th and 19th centuries throughout the world, and remains the leading single cause of death from an infectious disease in 2023.[1,2] However, stark socio-economic disparities apply as 99% of the current TB burden is found in LMICs, and within countries, TB affects the poorest and most disadvantaged.

Global burden

The WHO estimates that in 2023, 10.8 million people fell ill with TB (95% uncertainty interval [UI]: 10.1-11.7) and 1.25 million people died from TB (95%UI: 1.13-1.37).[1] There remains a gap in the detection and successful treatment of people with TB with only 76% notified and among them 88% successfully treated. Men accounted for 55% of notified cases, children and adolescents for 12% and human immunodeficiency virus (TB-HIV) co-infection for 6.1%. The South-East Asia and Western Pacific regi[32]ons accounted for 45% and 17% of notified cases. The estimated global incidence of TB in 2023 was 134 per 100,000 population (95% UI: 125-145).[1]

TB diagnosis

For over 100 years, the diagnosis of TB has been made using chest radiography or x-ray (CXR) for pulmonary TB and/or microscopy of a biological sample (sputum, tissue or fluid) using Ziehl–Neelsen or Auramine stain for mycobacteria that are 'acid fast bacilli.' Mycobacterial culture, which allows for the assessment of viable (and likely infectious) bacteria and drug susceptibility testing was developed in the 1930s. Culture and drug-susceptibility (C-DST) has been considered the gold standard for TB diagnosis and remains essential for surveillance, reporting, and as a reference standard in research. However, culture has significant limitations for clinical decision-making, particularly in high MDR-TB settings. Results typically take four to eight weeks to become available, creating critical delays in initiating appropriate treatment. This prolonged turnaround time often forces clinicians to begin empirical treatment without knowing the drug susceptibility profile, potentially leading to ineffective therapy, continued transmission, and development of further resistance. Moreover, C-DST has also had limited global application owing to the requirement of specialised laboratories, biosafety infrastructure, and trained staff, making it inaccessible in many LMICs and settings where TB burden is highest.

Since 2011, rapid molecular tests have been transformative by simplifying the diagnosis of TB and drug-resistance, allowing use at all levels of the health system, including lower level health facilities.[32–35] This rapid turnaround is particularly crucial in high MDR/RR-TB prevalence settings where early identification of drug resistance patterns enables prompt initiation of effective treatment regimens, reducing mortality, improving outcomes, and interrupting transmission of drug-resistant strains.[19,36] People diagnosed using tests recommended by the WHO - rapid molecular tests, lateral flow urine lipoarabinomannan assays, microscopy or culture - are defined as 'bacteriologically (or microbiologically) confirmed' TB.[37,38] These rapid diagnostics recommended by the

WHO are termed WRD and molecular tests that use nucleic acid amplification as mWRD. People diagnosed with TB in the absence of bacteriological confirmation are classified as 'clinically diagnosed.' Rapid diagnosis with bacteriological confirmation is important as it allows accurate diagnosis and the early initiation of effective treatment to improve individual outcomes and to reduce onward transmission.

TB Treatment

The mortality rate from untreated TB can be as high as 70%.[39] Effective drug treatments have been developed and available since the 1950s. The evidence for the current standard six-month combination treatment regimen for TB was established in the 1970s following a series of clinical trials demonstrated high (over 95%) treatment success rates.[40] This regimen consists of an intensive phase (2 months of isoniazid, rifampicin, ethambutol, and pyrazinamide) followed by a continuation phase (4 months of isoniazid and rifampicin) of oral medications available as a fixed-dose combination.[41]

Treatment for drug-resistant TB has historically been more complex and prolonged. Until 2016, MDR/RR-TB treatment regimens lasted 18-24 months and relied heavily on older, repurposed drugs including painful daily injections with significant toxicity and lower success rates (approximately 60% globally). Recently, several major breakthroughs have occurred with the development of novel TB drugs and newer MDR/RR-TB regimens that were shorter (6 to 9 months), all-oral regimens and clinical trials demonstrating effectiveness approaching that seen in drug-susceptible TB.[42–47]

TB and HIV

The intersection of the TB and HIV epidemics since the 1990s has contributed to an increase in the global TB burden. Globally, TB is the most common presenting illness and leading cause of mortality in people with HIV infection, accounting for 1 in 4 deaths.[1] HIV co-infection is the most powerful known risk factor for progression of TBI to active disease and people living with HIV are approximately 14 times more likely to fall ill with TB disease than people without HIV, irrespective of being on anti-retroviral treatment (ART).[48] HIV appears to be a modest risk factor for MDR/RR-TB.[49] Combination ART and TB preventive treatment (TPT) have been shown to have a significant impact in decreasing the risk of TB in HIV-infected populations and reducing the risk of death.[50,51] The bidirectional relationship between TB and HIV has led to WHO recommendations for integrated screening and prevention.[48]

TB risk factors and co-morbidities

The probability of developing TB disease varies significantly across populations due to host, environmental, and social risk factors that influence immune susceptibility and exposure patterns. Age is critical with children under 5 years and adolescents (10-19 years) at increased risk due to immature immune responses and increased social mixing patterns, respectively.[52,53] Older adults are at a higher population risk, due to their increased exposure to TB (i.e. a cohort effect).[54–56] Men have a higher incidence, prevalence and mortality from TB than women. These sex differences in TB burden, reflecting risk of TB infection and of TB disease, vary by age. Children and young adolescents under 15 years have similar risks of infection and disease for boys and girls. In older adolescents and adults, men (≥15 years) have 1.7 times higher TB incidence, prevalence and TB-related mortality than women.[1] This is likely driven by men having higher TB exposure risk and higher prevalence of co-morbidities that increase progression risk, as suggested by a recent systematic review and meta-analysis of population-based TBI surveys. There was little sex difference in TBI in children under 10 years; however, immunoreactivity conversion increased from adolescence, with the male-to-female infection risk ratio widening with age.[57]

Medical conditions create additional vulnerability**.** Malnutrition represents one of the strongest modifiable risk factors. A systematic review that included 27 million participants and 51 cohorts found that undernutrition probably increases the risk of developing TB two-fold (HR 2.23, 95% CI 1.83-2.72) in the short term (< 10 years) and may increase risk beyond 10 years.[58] Diabetes mellitus increases the risk of developing active TB by 1.9-4.2 times and is associated with MDR-TB and worse treatment outcomes.[59,60] Screening for diabetes is recommended for all people with TB, and an integrated approach is recommended by the WHO.[48]

Previous TB episodes increase recurrence risk substantially (RR 2.0 after the first episode, up to 17 after the fifth episode), while chronic lung diseases carry hazard ratios of 2.5-3.0. Pregnancy increases TB risk (incidence risk ratio, IRR 1.3-2.0) and TB in pregnancy is associated with adverse maternal and neonatal outcomes, including a two-fold increased risk of premature birth and 6-fold increased perinatal mortality risk.[61–63] Optimal approaches for integrated care, screening and prevention have not been established.

Mental health conditions including depression and schizophrenia significantly increase TB incidence through complex pathways involving immune dysfunction and socio-economic vulnerability.[64] Smoking, indoor air pollution, alcohol and substance use

increase TB risk and are associated with MDR-TB, poor treatment outcomes, and increased mortality.[65–67]

Socio-economic determinants are critical in determining a person's vulnerability to exposure, infection, disease and outcomes from TB.[68,69] TB must be addressed in its social context and by addressing these structural barriers to access and utilisation of services. Interventions recommended by the WHO and/or supported by evidence include nutritional support, social support, addressing co-morbidities, providing social protection and promoting access to universal healthcare.[70,71]

COVID-19 and TB

Progress toward global TB targets suffered an unprecedented setback owing during the COVID-19 pandemic. This was due to the indirect impacts that disrupted health systems and services, particularly in LMICs. The impact on TB services resulted in reduced case detection (18% in 2020), reduced treatment coverage (12% in 2020) and almost 700,000 excess deaths from TB from 2020 to 2023.[1]

Child TB

TB is an important preventable cause of child morbidity and mortality. In 2023, there were an estimated 1.3 million children and young adolescents (under 15 years) who developed TB and among them 187,000 died.[1] An estimated 80% of these deaths are in children under 5 years and almost all of these deaths occur in children who have not been detected and treated. The disproportionate TB burden in children is due to factors such as their clinical vulnerability (especially children under 5 years and/or malnourished), challenges in diagnosing TB and the sub-optimal uptake of preventive interventions (vaccination, nutrition, TPT).[72] However, if diagnosed and treated, children have a higher treatment success rate than adults-90% in 2022.[1]

Drug-resistant TB

Globally, there were an estimated 400,000 people who developed MDR/RR-TB in 2023, however only 44% of them were enrolled in treatment.[1] Globally, treatment outcomes remain poor with a success rate of 68%.[1] MDR/RR-TB transmission continues owing to these gaps in detection, treatment and prevention, referred to as the care continuum or 'cascade of care.'[18]

The true burden of MDR/RR-TB at the regional, national and sub-national levels is often unknown due to the lack of adequate diagnostics and surveillance, which requires molecular testing or specialised laboratories, equipment or trained healthcare workers.

Diagnosis of TB drug resistance requires testing using mWRDs, culture and drug-susceptibility testing (C-DST) and/or whole genome sequencing (WGS) techniques.

There remains no true point of care test for MDR/RR-TB that can be used outside a health facility with same day results.[73] The Xpert MTB/RIF (and now Xpert Ultra) have a turnaround time of two hours but requires electricity and some infrastructure. The lateral flow urine lipoarabinomannan (LF-LAM) is the only point of care WRD for active TB and does not detect drug resistance. It is used as a rapid 'rule in' test to initiate treatment and reduce early mortality and is currently only recommended in people living with HIV (PLHIV) and severely malnourished children.[37] There are more sensitive tests under evaluation in urine and blood.[74]

While MDR/RR-TB initially emerged from ineffective management of drug-susceptible (DS) TB, modelling predicts that the vast majority (96% uncertainty range 60-100%) of incident MDR-TB cases in high-burden settings now result from transmission.[75] This is supported by molecular epidemiology studies in several settings demonstrating clustering and epidemic spread.[76] Over the past 15 years, there have been major scientific and policy advances that have led to new tools and strategies for MDR/RR-TB. This includes the development and scale-up in LMICs of rapid molecular tests such as the Xpert MTB/RIF and Xpert Ultra assay as well as shorter, all-oral treatment regimens that are more effective than the longer regimens previously used, which were also associated with greater toxicity.[32,77]

TB Infection

Driving the global TB epidemic is the large pool of individuals who have had TBI (are immunoreactive) and are estimated to be one-quarter of the global population.[14] Approximately 5-10% of people with TBI will develop active TB disease during their lifetime, with the risk being highest within the first two years after infection, with most cases in high-burden countries resulting from recent rather than remote infection.[14,15,17,78,79]

The actual number of people with viable infections will be substantially lower due to self-clearance of infection. This is estimated in modelling studies to be 27-56% lower but would still result in over 800,000 people at risk.[78] Further, these individuals with viable TBI will have a higher lifetime risk of developing TB - 17%, compared with 12.6% assuming no clearance. The global prevalence of MDR-TB infection was estimated at 0.3% (95%UI 0.2-0.3) in 2014, with MDR-TB accounting for 1.2% of the total burden of

TBI.[80] This translates to almost 1 to 2 million people having a recent infection and being at high risk of developing active MDR-TB.

1.1.2 Global strategies to control and end TB

There have been three major global TB strategies developed by the WHO, each successively building on the previous frameworks while incorporating new scientific advances and transitioning from a purely medical approach to a more comprehensive, socio-economic and rights-based response to TB. See Appendix 1.1 for a summary of the objectives and targets of the WHO Global TB Strategies described below.

DOTS Strategy (1995–2005)

The WHO declared TB a global public health emergency in 1993 following a resurgence of TB, including outbreaks of MDR-TB in New York, where the cornerstone was a community-based program of directly observed treatment (DOT).[81] In response, it launched the DOTS Strategy (Directly Observed Treatment, Short-course), as a coordinated global and national programmatic response.[82] The DOTS Strategy was developed by The Union in the 1970s and focused on the diagnosis, standardised treatment and reporting of bacteriologically confirmed TB using smear microscopy – so the focus was on drug-susceptible TB. From 1995 to 2009, 41 million people with TB were successfully treated and it is estimated that 4.6 to 6.3 million lives were saved.[4] While there was substantial progress, the global targets set to detect 70% of new cases with sputum smear-positive pulmonary TB and to cure 85% of those detected by 2005 were not reached.[83] The challenges encountered included the impact of the HIV epidemic, the emergence and spread of MDR-TB, lack of adequate political commitment, insufficient funding and fragile or low-resilience health systems. The DOTS strategy did not address detection and management of MDR-TB, TB/HIV and all forms of TB (smear-negative TB).

Stop TB Strategy (2006–2015)

Recognising this, the WHO adapted to the DOTS-Plus approach, which addressed MDR-TB and eventually developed the more comprehensive WHO Stop TB Strategy (2006–2015).[82,84] This strategy was a significant expansion of the DOTS framework to include MDR-TB, TB-HIV, a focus on vulnerable groups (including children and household contacts), engaging the private sector, engaging with and empowering people with TB and communities, the promotion of research, strengthening of health systems and established new global mechanisms for technical assistance, laboratory strengthening and drug procurement. The vision and the global goal to eliminate TB by 2050 - defined

as achieving an incidence of less than one case per million population globally - was first established in 2006 as part of the Stop TB Partnership's Global Plan to Stop TB 2006-2015.[85]

However, the targets set to control TB and reduce TB incidence and mortality by 50% by 2015 (Stop TB) from the 1990 baseline were again not achieved.[27] These public health strategies had an insufficient approach to reduce TB transmission (and therefore prevalence and incidence) as they focused primarily on passive diagnosis and case management. A major gap was the lack of focus on preventive strategies.[86,87]

End TB Strategy (2016–2035)

In 2015, the United Nations (UN), as part of the establishment of the Sustainable Development Goals (SDGs), set a target to end the global TB epidemic by 2030.[88] The WHO's End TB Strategy (2016-2035) adopts a more comprehensive approach integrating patient-centred care, health systems, and research.[20] It places a stronger emphasis on universal health coverage, social protection and a rights-based approach. It is a complete overhaul of the public health strategies in DOTS and Stop TB strategies. End TB heralds a paradigm shift towards a strategy focused on accelerating transmission reduction towards TB elimination with a public health approach that prioritises case finding, treatment, care and enhanced prevention, including TPT.[27] The End TB strategy targets for 2035 are focused on reducing incidence (by 90%), mortality (by 95) and zero catastrophic costs, compared with the 2015 baseline. It does not set specific TB elimination targets at the global, national or sub-national level.

Progress and challenges

To date, the End TB strategy has yielded significant advances, including increased research, the development and implementation of new tools and models of care, strengthened civil society and partnerships between TB-affected community and policy makers partnerships.[5,6] Political commitment from countries has been strengthened, including through two UN high-level meetings on ending TB, in 2018 and 2023, with political declarations ratified and additional interim targets to enhance access to services and mobilise resources.[89,90]

Despite this, progress remains slow and insufficient and ending TB remains a distant goal. The COVID-19 pandemic caused unprecedented disruption to TB services, reversing progress on key indicators by approximately 12 years of progress.[91] There has only been an 8.3% decline in TB incidence from 2015 to 2023 (1% annual decline), far from the 50% target by 2025; and a 23% reduction in TB-related deaths against a 75%

target.[1] Informed by mathematical modelling, the End TB strategy recognises that the pathway to ending TB requires the combination of the optimisation of the implementation of existing tools and the development and deployment of new tools.[92] The key knowledge and implementation gaps are in the strategies and approaches for prevention.[87,93–95]

1.1.3 Strategies for TB and MDR-TB prevention

TB prevention framework

Interventions for the prevention of TB can be classified into the prevention of TB exposure and/or infection (primary prevention, targeting individuals without disease who are at risk) and the prevention of TBI progressing to disease (secondary prevention, targeting people with TBI). Interventions that address the socio-environmental determinants (housing, nutrition, social protection, and poverty alleviation) are considered primordial prevention, but may also work across primary and secondary prevention as well, such as nutrition.[68,96–99] Clinical and public health interventions to detect and treat people with TB through systematic screening may reduce onward transmission and therefore prevent TB exposure or infection. [100,101] Systematic screening involves the systematic identification of people at risk for TB disease in predetermined target groups, through symptom assessment and rapid testing, with the objective of early detection and treatment to reduce community-level TB prevalence. This section reviews prevention approaches, with particular focus on secondary prevention through treatment of TBI, which forms a central component of this thesis.

Infection control and prevention

Current tools and strategies for primary prevention are infection prevention and control interventions. Infection prevention and control interventions (environmental, administrative and personal controls–e.g. ventilation and air cleaning strategies, separating presumptive TB, masks) are recommended in higher risk, indoor settings such as health facilities, congregate settings (prisons) and TB-affected households.[26,102–104]

Vaccination

Vaccination has the potential to prevent both infection and disease progression. The Bacille Calmette-Guérin (BCG) vaccine was developed over 100 years ago and remains the only licensed vaccine against TB.[105] BCG is typically administered at birth or in early infancy as part of the Expanded Programme on Immunisation in high TB-burden countries. Its primary value lies in preventing severe forms of TB, including tuberculous

meningitis and miliary TB, in young children under 5 years, with limited effect on older children, adults, pulmonary TB and overall TB transmission. In two recent meta-analyses, BCG demonstrated an overall effectiveness of 18% against all types of TB disease (incident and prevalent) and 37% for children under 5 years old.[106] It also showed an effectiveness of 35% in preventing TBI in household contacts but was inconsistent across other groups. Promising new TB vaccine candidates are under development. The M72/AS01E vaccine, which is in a Phase III trial, along with five other candidates, target either the prevention of infection and/or the progression of infection to disease.[107–113]

TB preventive treatment

TB prevention strategies in this thesis will focus on the treatment of TBI (or TB exposure in high-risk cases, such as household or close contacts) with antibiotics which reduces the risk of TB infection progressing to active TB disease and is referred to as TPT (and previously referred to as chemoprophylaxis). This is integrated with screening and detection of active disease, for example, when investigating household or close contacts of people with bacteriologically confirmed TB (the index cases) and may include testing for TBI. A contact is any person who has been exposed to a person with TB disease and is operationally defined. Contact investigation for TB involves screening and management of household and other close contacts of bacteriologically confirmed pulmonary index cases.[114]

TPT has been recommended since 2009 by the WHO for two high- risk groups, young children (under 5 years) who are contacts and PLHIV without the need for a test for TBI.[115,116] Young children and PLHIV have a high risk of morbidity and mortality from TB after exposure.[52,117,118] However, young children do not make a major contribution to onwards transmission of TB.[119,120] Despite the clear benefit of TPT to young child contacts, PLHIV and individuals with TBI, TPT has not been implemented or expanded at scale. The barriers to this include prioritisation from programs given perceived feasibility and cost, health care worker perceptions of limited benefit, concern regarding development of resistance, lack of access to and turnaround times for tests for TBI, access and the lack of community-based models of care, and longer regimens that require adherence and support.[121,122]

Treatment regimens for TPT currently involve isoniazid or rifamycin-based regimens of between 1 to 6 months' duration that treat exposure to drug-susceptible.[9]

TPT for MDR-TB

Evidence to guide TPT following MDR/RR-TB exposure until 2024 was limited to observational studies.[123,124] In 2024, the results of clinical trials were published that demonstrated the effectiveness of 6 months of levofloxacin for household contacts of MDR/RR-TB that is fluoroquinolone susceptible (i.e. not pre- or XDR-TB) index cases, and this evidence has already informed updates to WHO recommendations.[9,125–127]

Importantly, community-wide TPT has the potential to reduce the incidence of TB. Seminal studies from the pre-MDR-TB era and modelling suggest that combining the detection and treatment of active TB and TBI results in a more rapid and sustained reduction of TB incidence in the community than active case detection alone.[128,129] While the efficacy of TPT for TBI has long been established, programs in high-burden settings have not prioritised nor implemented it at scale.[122]

The emergence and transmission of MDR-TB continues to be a major obstacle to achieving the goals of TB elimination.[75] This challenge is particularly acute in settings like Western Province, Papua New Guinea (PNG), where high transmission rates, fragile health systems and limited resources create complex implementation barriers. The elimination of MDR-TB in specific locations is a goal in its own right and arguably one of the most important steps towards TB elimination.[18] TB elimination at a national or sub-national level cannot be achieved without a strategy to address TBI, and this also applies for MDR-TB.[75]

Until recently, there has been a lack of evidence to develop recommendations for TPT regimens for people exposed to MDR-TB (drug-resistant TBI). Observational data supported the use of 6 months of levofloxacin as TPT for household contacts exposed to MDR-TB, and the results of two clinical trials confirmed this as an effective intervention in 2024, leading to a change in WHO guidance.[123,125] Acceptable, feasible and effective interventions and models of care for high-burden MDR/RR-TB settings involving a comprehensive detect, treat and prevent approach are required. Knowledge and implementation gaps exist in the optimal strategies for screening and delivering TPT (including the regimens), in particular in high-burden MDR-TB settings.[130] This gap has been particularly challenging in high-transmission settings where standard approaches based on known exposure may be insufficient.

These implementation gaps in high MDR-TB burden settings create an urgent need for research to develop and evaluate comprehensive approaches that integrate detection, treatment, and prevention strategies. This thesis addresses this need by evaluating such

approaches in a high-burden, remote setting where traditional TB control measures have proven insufficient to interrupt transmission. Research embedded in public health responses within fragile health systems, conducted with in collaboration with established partnerships provides unique opportunities to test innovative models of care that can inform broader implementation efforts.

1.2 The setting: Western Province, Papua New Guinea

1.2.1 Papua New Guinea

PNG is a LMIC, ranking the lowest in the Western Pacific on the Human Development Index and 154th out of 193 countries globally.[131,132] It is the largest landmass and most populous country in the Pacific with an estimated population of over 11 million people.[133] It was colonised by the United Kingdom, Germany and Australia before gaining independence in 1975 and maintains a strong partnership with Australia. The Indigenous peoples of PNG are Melanesians, and it is one of the most culturally and linguistically diverse countries in the world with over 800 languages and distinct ethnic groups. The average life expectancy is 66 years, with large populations in the younger age groups. PNG received 2.2% of its gross national income from overseas development assistance (foreign aid) in 2022.[131]

PNG was one of two countries not to achieve any of the Millennium Development Goals in 2015, and progress towards achieving the health SDGs has been slow or stagnant. The PNG health system is fragile with challenges such as sustained domestic financing, shortages of human resources and essential medical supplies, fragmentation and governance issues from the decentralisation of management and limited access to healthcare for 86% of the population who live in rural areas owing to remoteness and topography.[132] The coverage of essential health services is about 33%, as the health workforce density remains low (15 per 10,000 population).[131,134] Although there is an increase in noncommunicable diseases, the pressing health issues remain the gaps in basic maternal and child health services, immunisation and communicable disease control.[135]

1.2.2 Western Province

Western Province is the largest, most sparsely populated, and most remote of PNG's 22 provinces (see map, Figure 1.1). Its population is estimated at 315,273 in 2021, over an area of approximately 98,000 km^2.[133] The remoteness and limited roads make access to and delivery of health and essential services even more challenging than in other

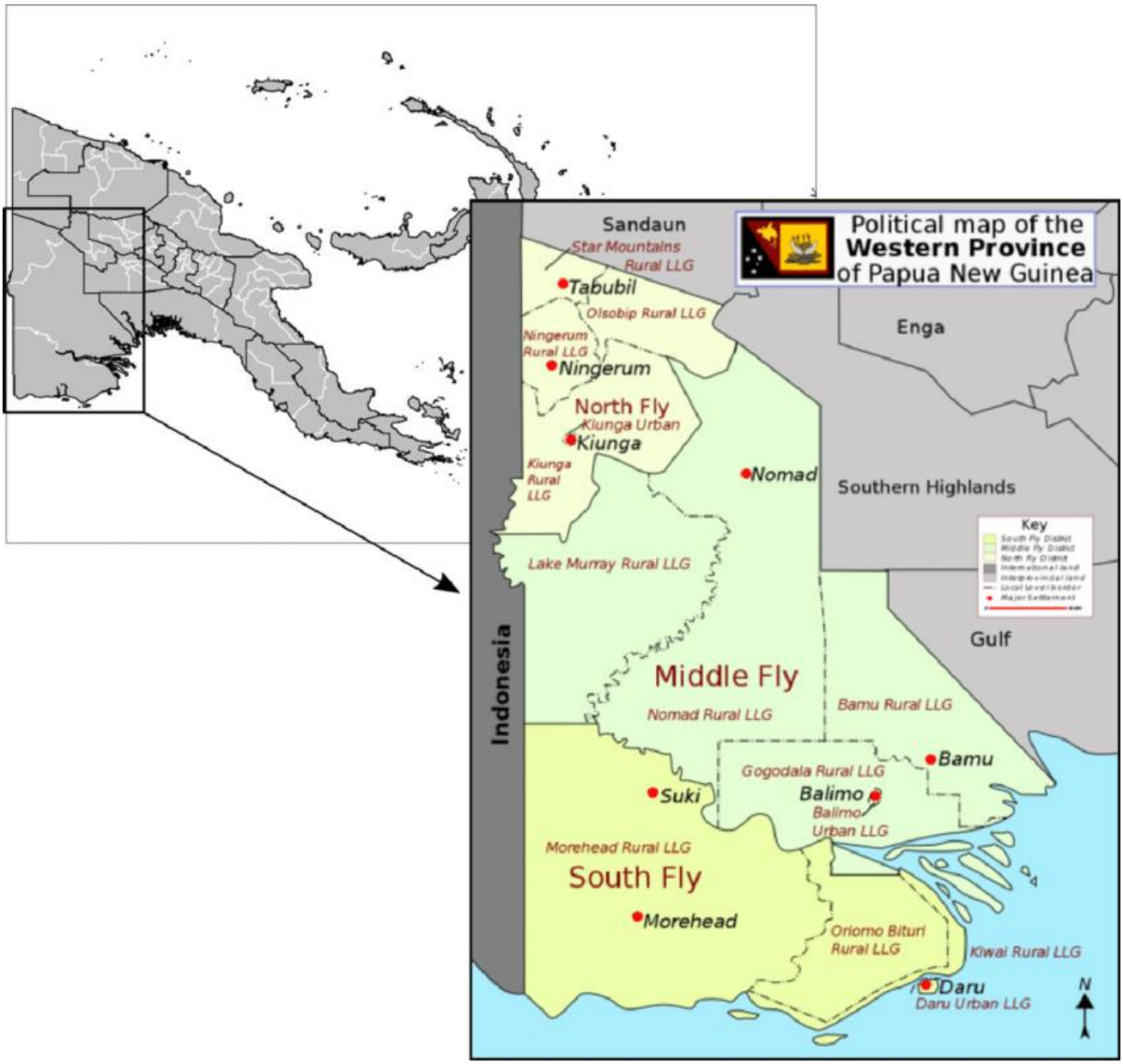
provinces. Health indicators, where available, are some of the worst in PNG. For example, the measles immunisation coverage ranged from 16% to 37% from 2019 to 2023.[134]

The Fly River divides the province into three districts: North Fly, Middle Fly and South Fly (SFD). A fourth district, Delta Fly (DFD) was newly established in 2022 comprising of the Gogodala and Bamu rural local level government areas of MFD (see map,

Figure 1.2). Western Province has many small and remote villages, however, has high rates of urbanisation compared with the rest of PNG, particularly the provincial capital of Daru, located in the SFD.[136]

Daru is an island (land area 15 km^2) with an estimated population 19,397 residents in 2021 and is 100km from the Australian Maritime border in the Torres Strait.[133] Daru Island is the main residential and service town in SFD, and parts of Delta Fly District. It is notably crowded for a small island with a reported average household size 7.5; however, with informal settlements and migration, this is likely higher.[133] Economic development is limited, with a multi-dimensional poverty index (measuring household poverty) that is comparable to rural Afghanistan and Sudan, particularly in South Fly.[137]

Figure 1.1 Map of Western Province, Papua New Guinea (2017)



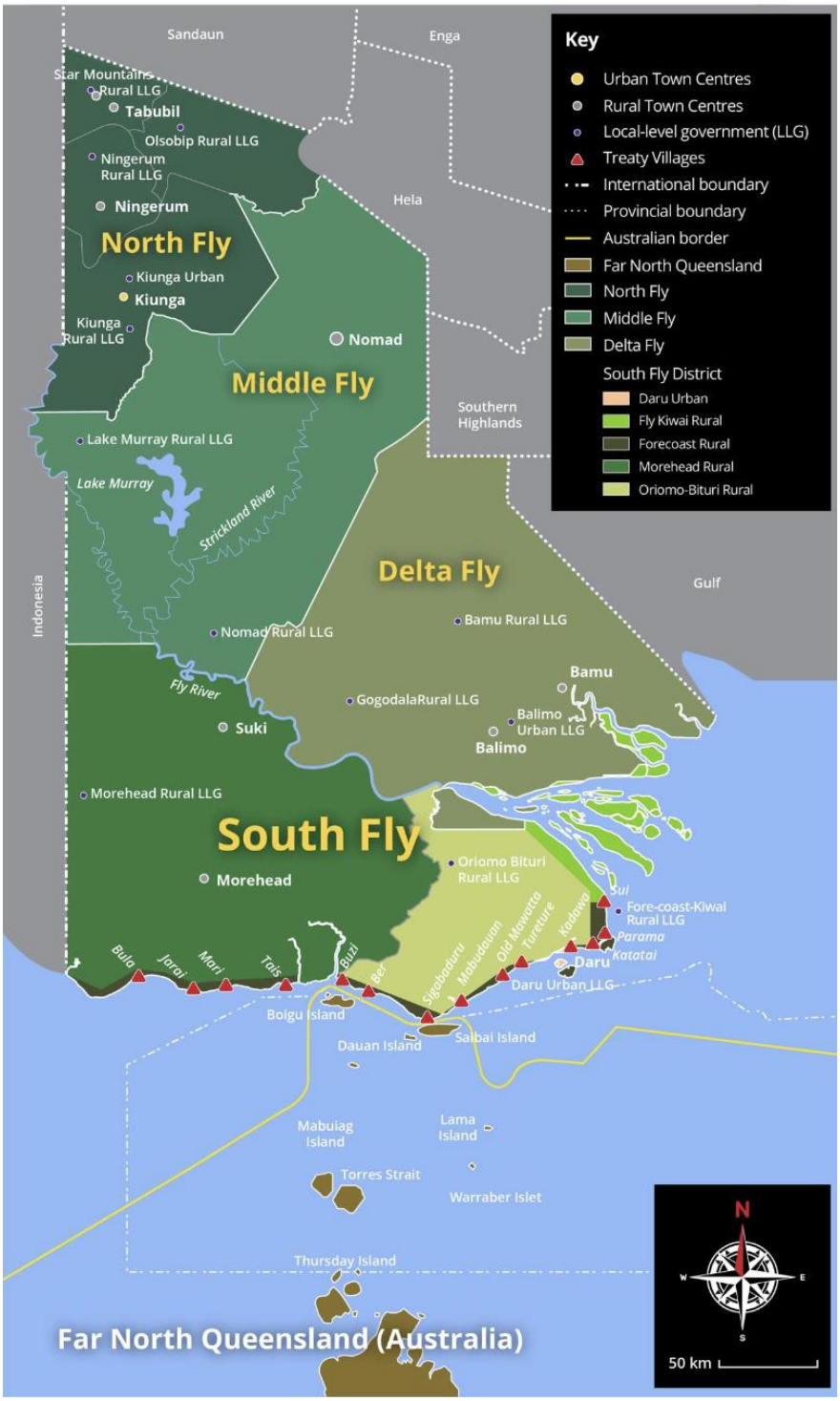
Source: Adapted by Diefenbach-Elstob et a.l[138] , from Wikimedia Commons images.

The province has two international borders: a land border with Indonesia to the West and a maritime border with the Australian Torres Strait to the South (see Figure 1.3). The closest Australian Islands are 5 km from the PNG coastline. The Melanesian communities of SFD, Australia's Torres Strait and West Papua (Indonesia) are historically, culturally, socially and economically linked– described by Moran et al. as the Torres-Strait Trans Fly borderland (see map, Figure 1.3).[139,140] The Torres Strait Treaty was established following PNG's independence in 1975 to protect the way of life of the 'Traditional Inhabitants', conserve the environment and promote sustainable development.[137] A protected zone (Figure 1.3) has been established encompassing 14 PNG villages and 14 Australian Torres Strait Island communities which allows for free movement without passports for traditional activities (e.g. fishing) and access to government services (e.g. health centres and services). There are no specific human health or biosecurity provisions in the treaty; however, since 2000, a series of increasingly stringent restrictions have been applied to PNG nationals crossing the border, owing to the concerns of infectious diseases, including TB and MDR-TB.[139]

A major determinant of health and development in Western Province has been the Ok Tedi Mine in the North Fly District, an open-pit copper and gold mine that commenced operations in 1984. The Ok Tedi Mining Limited (OTML) has contributed close to 20% of PNG's government revenue and has substituted for the provincial government in the providing public goods, such as roads, schools and health services.[137]

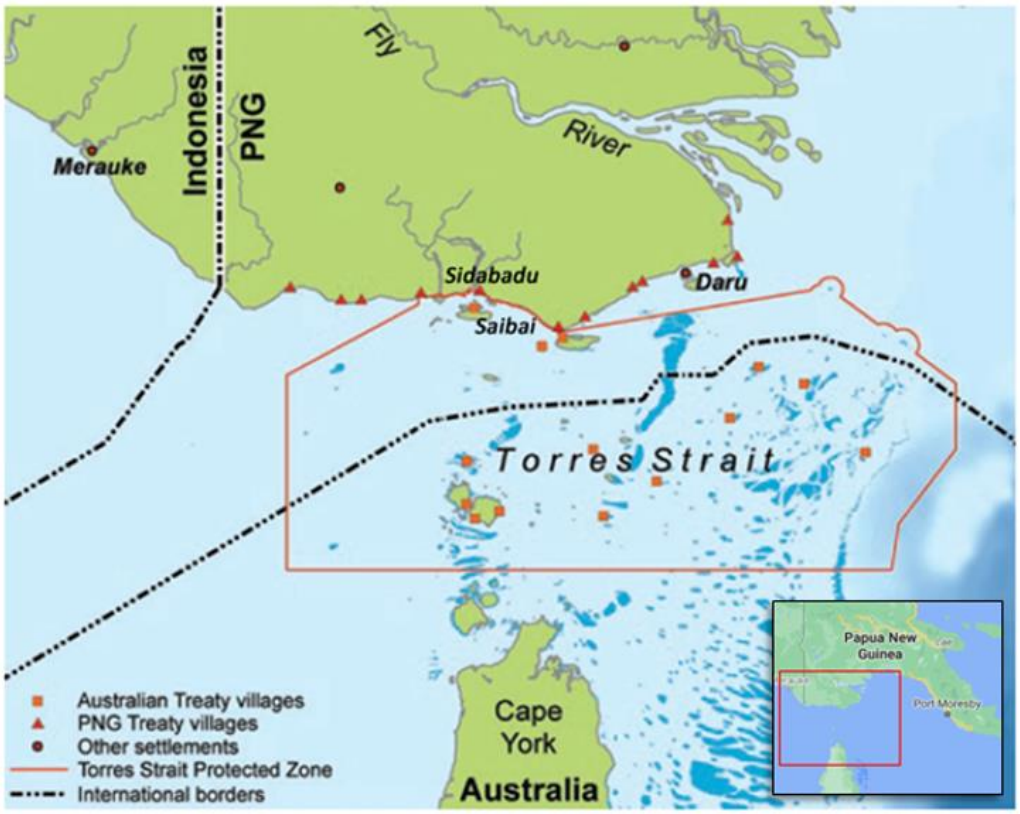
In 1999, OTML reported major environmental damage through the discharge of huge quantities of waste into the Fly River. This resulted in the loss of fish populations, vegetation and the livelihoods of many local communities, some of whom migrated to Daru. This was further compounded by temporary movement to Daru for access to compensation payments, which occur several times each year.[139] The population fluctuates throughout the year as people from mainland villages arrive in Daru to access services and mining compensation payments, but the exact extent is not known.[137]

Figure 1.2 Map of Western Province, Papua New Guinea (2022)



Source: PNG-Australia Western Province Strategy 2022 to 2030[136]

Figure 1.3 Map of the transboundary region between Papua New Guinea, Australia and Indonesia.



Source: Busilacchi et al., CSIRO [137]

1.2.3 The health system in Western Province

The governance and organisation of the health system in PNG are decentralised, with provincial and local level governments holding responsibility for primary and secondary health service delivery and public health functions.[132,135] Service delivery is supplemented by Church-based health providers, and to a lesser degree, employer health services and a small private sector. There is also a large and informal traditional health sector. The National Department of Health (NDoH) oversees the health system, sets policies and standards, provides technical guidance and is responsible for medical supplies, health information systems and monitoring and evaluation. Through the *PHA Act of 2007*, Provincial Health Authorities have been established to merge the curative (provincial hospitals, NDoH) and population health divisions (Provincial Health Office) under one administrative structure.[141] The Western Provincial Health Authority (WPHA) was established in September 2019. Daru Provincial Hospital (DPH, formerly Daru General Hospital) is the provincial referral hospital (level 5) for Western Province and people who cross the Torres Strait international border.

The remoteness and limited road access make access to and delivery of health and essential services extremely challenging in Western Province. Health indicators, where available, are amongst the worst in PNG. For example, from 2018 to 2023 the measles vaccination coverage in Western Province has been below 30% (WPHA reports). Within this challenging health system context, TB has emerged and thrived as a major crisis.

1.3 Tuberculosis in Western Province, Papua New Guinea

TB burden and recognition of MDR-TB

TB is a major public health issue and a leading cause of death in PNG, affecting all age groups.[142] PNG is classified as a high-burden country for TB and MDR/RR-TB by the WHO with an estimated incidence of 432 per 100,000 people (uncertainty interval 348–525), TB mortality of 31 per 100,000 people (uncertainty interval 14–43) in 2023.[1] The emergence and transmission of MDR/RR-TB in PNG is a major challenge with recognised hot spots in the National Capital District (NCD, Port Moresby) and SFD of Western Province.[143,144]

The first report of MDR/RR-TB in PNG was from an audit of TB case notifications from clinics in the Australian Torres Strait Islands which are on a maritime border with SFD and showed a dramatic increase in cases in PNG nationals between 1998 and 2002.[145] Subsequent reports from the Torres Strait demonstrated alarming rates of MDR/RR-TB with evidence of person-to-person spread or primary transmission in PNG.[146] In late 2011, Queensland Health commenced the transfer of care for 92 PNG nationals with MDR/RR-TB to the provincial hospital, DPH in SFD. This was in conjunction with specific financial support from the Australian Government to improve the management of TB in Western Province through the provision of clinical staff, a community engagement partner and the establishment of key infrastructure and service agreements (communications centre, TB ward, drug supply, laboratory support and an outreach boat). Case notifications of MDR/RR-TB in Daru increased each year from 59 cases in 2012, to 61 in 2013 and 84 in 2014.[147] In 2013, SFD reported TB case notification rates that were almost twice as high as the national rate. A molecular epidemiology study confirmed a unique circulating outbreak MDR-TB strain in Daru.[148] Treatment success rates for DS-TB and MDR/RR-TB in 2013 were 65% and 50%, respectively (National TB program reports).

Emergency Response and programmatic interventions

Recognising alarming rates of MDR/RR-TB, the emergence of extensively drug-resistant TB and the need for a concerted programmatic response, the PNG National Department

of Health (NdoH) convened an Emergency Response for MDR-TB in Western and other 'hot spot' provinces-Gulf and NCD in August 2014. The emergency TB response and program have been led by the WPHA and implementation partners supported by the Australian Government: Burnet Institute, a research and public health agency, for TB technical and implementation support, strategic planning and evaluation, health systems strengthening, community consultation, data utilisation, and operational research; and World Vision, an international community-based organisation, for community engagement and care.

While the scope of the TB program was provincial, the focus of this emergency response in Western Province was SFD and centred on initially Daru Island where the DPH was providing MDR-TB diagnosis and treatment with an overwhelming caseload. The programmatic TB response, or public health project, is referred to as the SFD TB program and includes the technical assistance and implementation research projects conducted through the Burnet Institute.

TB diagnosis is centralised at DPH, and treatment of MDR/RR-TB varied over time according to WHO and PNG guidelines. Newer TB drugs (bedaquiline, delamanid) were introduced systematically in Daru in 2016, the first site in PNG, along with an electronic medical record system for clinical management and TB surveillance.[149] A community-based model of care was established utilising community health workers, task-shifting models and patient support including nutrition, education and counselling.[150] The response from 2014 to 2022 is evaluated in Chapter 3, where detailed clinical and programmatic methods are provided.

Household contact investigation of bacteriologically confirmed pulmonary TB index cases was introduced in 2016 with symptom screening and provision of TPT for young (<5 years) child contacts of index cases with DS-TB from 2016 and MDR/RR-TB from 2019 to 2020 (evaluated in Chapter 5). A systematic screening initiative for community-based active TB detection was conducted from 2018 to 2019 (detailed in Chapter 3).[151]

Community engagement and education have been central components of the TB program response since 2011, with World Vision providing health promotion and social mobilisation activities focussed on enhancing detection and treatment support for active TB. This was strengthened from 2014 when Burnet Institute introduced person-centred care initiatives and partnerships with people affected by TB. A peer counselling model was introduced in 2016 involving people who have been affected by, living with or having survived TB, known as PALS, who are trained and mentored to provide education and

counselling support.[150] Community engagement activities are detailed in Chapter 3, with a description of patient TB care journeys and socio-ecological dimensions of TB in Chapter 4.

Building on the initial qualitative research that forms Chapter 4, comprehensive studies have been conducted in collaboration with the PNG Institute of Medical Research to understand the lived experiences of people with TB and their households in Daru from 2019 to 2022.[152–155] The research was led by PNG social scientists, with international support and in collaboration with the provincial TB program.

While the emergency response has resulted in improved case detection and treatment outcomes (Chapter 3), the burden of TB in SFD, and specifically in Daru, remains extremely high. The current approach requires significant resources (both financial and human) just to contain the epidemic, with major costs to patients, their families and healthcare services. The TB program, while effective in improving patient outcomes, is not sustainable for the health system to absorb in its current form.[153] Given the persistent high burden of TB and MDR/RR-TB and the global vision of ending TB, it is imperative that evidence-based strategies and interventions are designed and implemented to interrupt transmission and achieve reductions in TB incidence, rather than mere containment. This thesis addresses this critical need by designing and evaluating the implementation of comprehensive approaches that combine enhanced TB detection and treatment with innovative prevention strategies in this high MDR/RR-TB-burden, remote setting (Chapters 5-7).

1.4 Research objectives and significance

1.4.1 Aims and objectives

This thesis aimed to address the policy-practice gap and generate evidence to reduce the burden of TB, including MDR/RR-TB in a remote setting in PNG, with applicability to other high-burden MDR/RR-TB settings.

The specific objectives were to:

1. Describe the characteristics of people with TB and programmatic interventions for TB and MDR/RR-TB.

2. Evaluate detection and treatment outcomes and factors associated with unfavourable TB outcomes, including MDR/RR-TB.

3. Describe and identify influencers of the health seeking and service utilisation journey of people diagnosed with TB, including MDR/RR-TB.

4. Evaluate the implementation of community-based household contact investigation and provision of TPT for young children (<5 years) contacts of people with TB, including MDR/RR-TB.

5. Design the implementation and evaluation of a comprehensive community-wide intervention that combines screening, detection of active TB with the testing and treatment of TBI, including MDR/RR-TB.

1.4.2 Research approach

According to the WHO, 'operational research' refers to using scientific methods to analyse and improve the efficiency and effectiveness of existing health programs by examining routine data, while 'implementation research' focuses on studying how to effectively put evidence-based interventions into practice within a healthcare system to reach a wider population, often involving research on scaling up programs and addressing barriers to adoption; both are crucial tools for improving health outcomes globally.[156]

Three operational / implementation research studies were conducted and embedded in the programmatic TB response in Daru, South Fly District, Western Province to evaluate interventions for detecting, treating and preventing TB, including MDR/RR-TB from 2014

to 2022. This led to the design of a novel comprehensive community-based TB screening and prevention study protocol from 2021 to 2023.

I led the establishment of systems for analysing routine program data for operational research, including baseline assessments and evaluations, as new tools and strategies were introduced over time. The first study involved a retrospective quantitative analysis, and the second prospective qualitative analysis, as the program developed detection and treatment approaches for TB. The third study involved prospective implementation research on contact investigation for TB and TPT. This led to the design of an implementation research protocol for a comprehensive community-based strategy to detect, treat and prevent TB.

The research undertaken for this thesis represents a collaborative approach and effort. I have had a leadership role in this response as technical director of Burnet Institute's *Reducing the impact of drug-resistant TB in Western Province* (RID-TB) project[157] from 2014 until 2021 where I provided advice, implementation support, systems strengthening and capacity building to the WPHA in the design, implementation and evaluation of the TB response and program in SFD, through a project team based in PNG and Australia. Additional research grant funding was obtained to complement the RID-TB and WPHA TB program objectives and supports projects outlined in this thesis. This included an operational research capacity building initiatives using the Structured Operational Research Training Initiative (SORT-IT).[158] I had responsibility for a team based in Daru, which included clinical and public health specialists, community health workers and research staff who worked in partnership with the WPHA. My primary supervisor provided technical and strategic advice on clinical and public health implementation, both prior to and throughout the undertaking of this PhD, support for the partnership development with stakeholder engagement, as well as operational research training guidance for the research activity and procurement of grant funding.

The RID-TB project and my own approach to public health and research prioritise local leadership and program stewardship by the WPHA. Therefore, the research questions for this thesis were designed in partnership with the stakeholders from the SFD and National TB programs in PNG, and were conducted in collaboration with TB program staff, researchers and provincial and national governments in PNG. This research program and PhD were built on a series of collaborative projects and grants funded by the Australian government, aimed at improving health outcomes for MDR-TB in PNG and addressing health security threats. Importantly this included operational research capacity building initiatives that were embedded in the SFD TB program and response.

1.4.3 Significance

The detailed evaluation of the TB response in SFD and the implementation and evaluation of a comprehensive strategy that adds prevention to detection and treatment interventions for TB, including MDR/RR-TB has significant potential practice and policy impact and relevance, nationally and globally. The TB and MDR/RR-TB burden in SFD is one of the highest reported at a sub-national level. This thesis examines the hypothesis that to have a significant impact on the incidence of TB in Daru, SFD, the use of prevention strategies, specifically focused on TPT, will need to be extended beyond household and close contacts to the wider community. This is a novel approach that operationalises the WHO End TB strategy and is a priority for local and national governments in PNG.

Given the specific socio-cultural context and fragile health system, this thesis generates new knowledge that is specific to SFD and is necessary to establish an acceptable and effective community-based and integrated model for detecting, treating and preventing TB, including MDR/RR-TB. This research will provide critical evidence for SFD with applicability to other parts of PNG, similar contexts globally and high burden MDR/RR-TB settings.

1.5 Structure of thesis

This thesis consists of eight chapters as follows:

- **Chapter 1** serves as an introduction, explain the background, providing key definitions, describing the setting in which the research was conducted, and outlining the research aims and objectives.

- **Chapter 2** is a narrative literature review of the public health approaches to reducing TB transmission focussed on systematic screening, contact investigation and TPT. This review establishes the evidence and policy basis on which this thesis builds. The review provides an overview and analysis of the major topic areas presented in subsequent Chapters 3 to 7.

- **Chapter 3** is a retrospective cohort study that evaluates TB detection and treatment in SFD, and factors associated with unfavourable outcomes from 2014 to 2022.

- **Chapter 4** presents a qualitative study of the socio-ecological determinants and treatment experiences of people with TB and their contacts conducted in 2018.

- **Chapter 5** is a prospective implementation study of community-based TB contact investigation including the provision of TPT to young child contacts of people with TB, including MDR/RR-TB from 2017 to 2020.

- **Chapter 6** is a critical reflection and analytic summary of programmatic lessons learned from contact investigation from 2017 to 2022 and provides the rationale for the innovative aspects of the protocol in Chapter 7

- **Chapter 7** presents a research protocol for a prospective mixed-methods implementation study of a comprehensive, community-wide intervention to detect, treat and prevent TB, including MDR/RR-TB. It was developed from 2021 to 2023.

- **Chapter 8** presents a discussion that provides an overview of the thesis' main findings, key limitations, challenges and lessons, as well as a perspective on the significance and future implications of this thesis for public health strategies aimed at ending TB in a high-burden MDR-TB setting.

Chapter 2: Literature Review: Public health approaches to ending TB

2.1 Introduction and key concepts

This narrative literature review examines the evidence base for public health approaches to reducing TB transmission, with a focus on systematic screening and TPT strategies. These interventions, when implemented together as part of a comprehensive 'detect-treat-prevent' approach, represent key components of the WHO End TB Strategy and offer the potential to interrupt TB transmission in high-burden settings.[20]

The review synthesises literature published until June 2025, while acknowledging that the knowledge and evidence base for TB interventions has evolved over the course of this thesis. As such, each chapter reflects the evidence available at the time of its conduct (2014-2023). Of note, the WHO guidelines for TPT for contacts exposed to MDR/RR-TB underwent major updates in 2020 and 2024.[9,159] This review will focus on high-TB incidence settings (see Key Definitions) with low-moderate HIV prevalence, given the relevance to South Fly District, Papua New Guinea.

2.1.1 The Spectrum of TB infection and disease

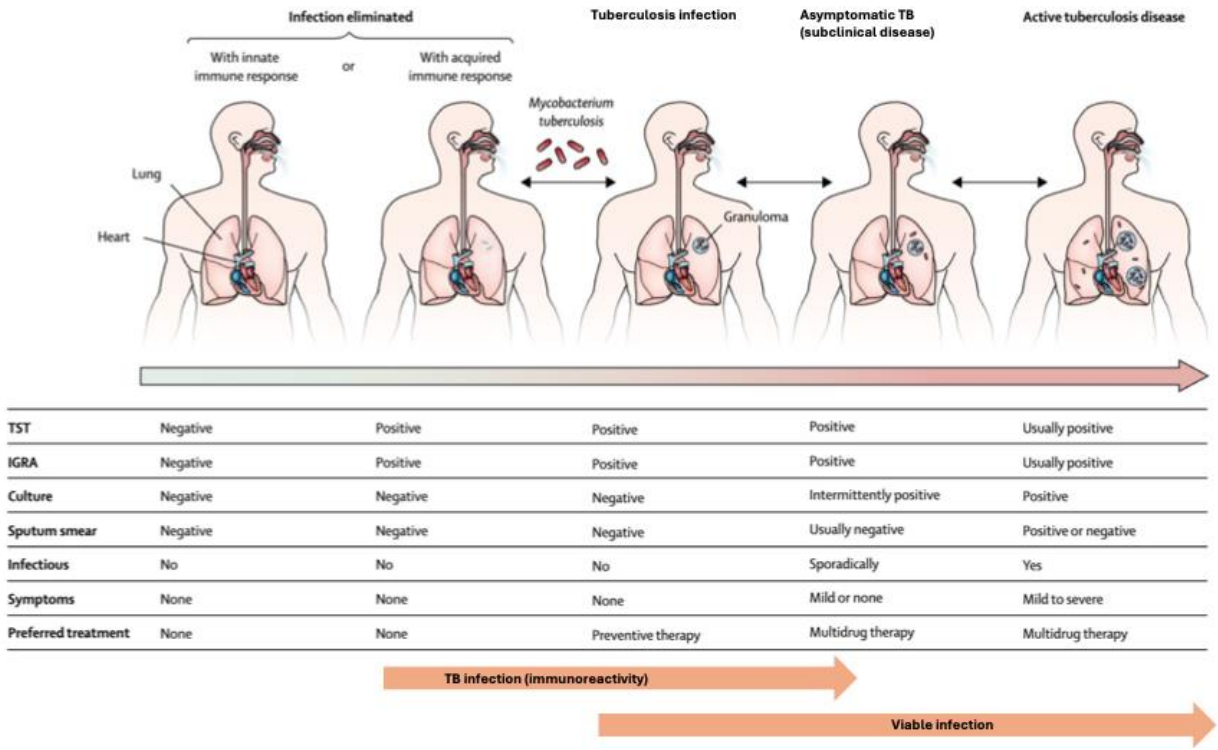
The traditional dichotomous model of TB—distinguishing only between latent infection and active disease—has given way to recognition of a dynamic spectrum resulting from complex host-pathogen interactions.[160] This conceptual shift fundamentally shapes modern approaches to TB control, as it recognises that individuals exist along a continuum from early clearance of *M. tuberculosis*, through contained infection, to subclinical and symptomatic disease **(**see Figure 2.1).

This spectrum model has critical implications for public health interventions. Subclinical TB—where individuals have active disease without symptoms—challenges traditional symptom-based screening approaches and may contribute substantially to ongoing transmission.[161] Studies from TB prevalence surveys demonstrate that around 50% of bacteriologically confirmed TB cases are asymptomatic, with CXR detecting 89% of these cases that would be missed by symptom screening alone.[13,162]

The heterogeneous progression pathways and variable incubation periods (from weeks to decades) create both challenges and opportunities for prevention.[163] While only 5-

10% of infected individuals will develop disease in their lifetime, the risk is highest in the first two years following infection—a critical window for preventive intervention.[10,16,164]

Figure 2.1 Spectrum of TB infection and disease

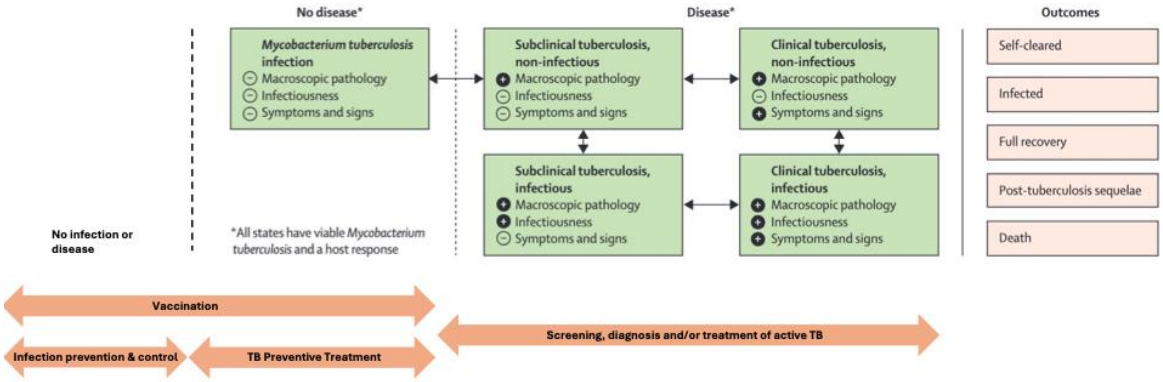


Adapted from: Pai M, Behr M, Dowdy D, et al. Tuberculosis. Nat Rev Dis Primers[160]

This understanding underpins the rationale for both systematic screening to detect all forms of disease across the spectrum, and TPT, to interrupt progression in those with TBI. Importantly, recent work, including an international Delphi consensus exercise by Coussens et al. that developed the TB Infection Cascade-of-care Epidemiologic (TB-ICE) framework, distinguishes between persistent immunoreactivity from cleared infection versus viable infection that may progress to disease—a distinction critical for targeting TPT strategies effectively.[10,12,55,165]

Figure 2.2 illustrates the conceptual states of TB infection and disease, adapted from the TB-ICE framework, depicting where different interventions—infection prevention and control, vaccination, screening, treatment, and preventive therapy—target specific stages across the TB spectrum.[12] This framework demonstrates how a comprehensive approach requires interventions at multiple points to effectively interrupt transmission and prevent disease progression.

Figure 2.2 Conceptual states of TB infection and disease and TB interventions



Adapted from: Coussens, Esmail, Houben et al. Lancet Resp Med 2024[12]

The following sections examine how systematic screening and preventive treatment interventions can be optimised to target different points along this spectrum in high-burden settings, with attention to both the evidence base and implementation considerations.

2.2 Systematic screening for TB

Systematic screening for TB or active case finding (ACF) is provider-initiated detection of TB disease conducted in pre-determined risk groups, settings or in the general community (community-wide screening).[166] The process involves screening for TB, followed by diagnostic testing and/or clinical evaluation for those who screen positive, and linkage to care for those diagnosed with TB. Systematic screening for TB identifies people with active TB and can also identify people eligible for TPT when active TB has been excluded. The objectives of TB screening are to (1) reduce the impact of TB on the individual (morbidity, mortality, post-TB complications and socio-economic consequences) and (2) reduce the impact of TB on community prevalence by preventing the onwards transmission of TB.[167] For TB screening to have benefit and impact, it must include effective linkage to diagnosis, treatment and care, including for drug-resistant TB.[101,168,169] Broadly, systematic screening can be conducted in the general population (community-wide screening) or in targeted groups and settings, including contacts of people with active TB (contact investigation).

2.2.1 Current WHO guidelines

The most recent WHO guidelines (2021) recommend systematic screening in the general population when TB prevalence is >0.5% (community-wide screening) or in targeted

groups, sub-populations or settings at higher risk for TB, as outlined in Table 2.1.[167,170] These risk groups either have individual-level (e.g. medical) risk factors and/or live in settings or sub-populations with structural risk that increase TB transmission risk – e.g. inadequately ventilated indoor environments and overcrowding.[171]

Household and/or close contacts of people with TB are a particularly important group for screening due to their high risk of exposure, TB infection, disease and consequences.[36,164,167] Contact investigation refers to systematic identification of TB disease and/or TBI among people who have close contact with an "index" person and/or settings where exposure has been identified. The process includes screening and management; diagnostic testing and/or clinical assessment and provision of appropriate treatment for TB disease or TPT for those without TB disease and who are eligible.[170]

Screening PLHIV for TB at each clinical visit, has been a WHO recommendation since 2011, due to their increased risk of developing TB disease.[172]

Table 2.1 WHO recommended groups, sub-populations and settings to be systematically screened for TB (2021)

Potential site of screening	**Risk group**
Community	General population in areas with an estimated TB prevalence of ≥0.5%
	Sub-populations with structural risk factors for TB – urban poor, homeless, remote or isolated areas, Indigenous, migrants, refugees, internally displaces persons and other at-risk groups with limited access to care
	Household contacts or other close contacts of individuals with TB disease
Health care	In settings where the TB prevalence in the general population is ≥100/100,000: people with a risk factor for TB[1] who are either seeking health care or who are already in care
Workplaces	Health care workers Current and former workers of workplaces with silica exposure
Residential institutions	Prisons and penitentiary institutions People living in shelters

[1]Risk factors for TB include malnourishment, previous TB, chronic lung disease, smoking, fibrotic lesions on chest X-ray, diabetes mellitus, alcohol use disorder, substance use disorder, pregnancy, immunocompromising conditions

Source: World Health Organisation[167,170]

WHO recommends specific tools-symptom screen, chest X-ray and/or mWRDs - for systematic screening for TB disease according to age and risk group as shown in Table 2.2.[167] PLHIV are recommended to have diagnostic evaluation using mWRDs or lateral flow urine lipoarabinomannan assay (LF-LAM).[37,173]

Table 2.2 WHO recommended tools for screening for TB disease by age and risk group (2021)

Group	Recommended screening tool
≥15 years	Symptom screen, CXR or mWRDs alone or in combination CXR with computer aided detection software may replace human readers
<15 years who are household or close contacts	Symptom screen, CXR or both
≥ 10 years (adolescents and adults) with HIV	WHO recommended four symptoms screen, CRP, CXR, mWRDs
<10 years (children) with HIV	Symptom screen

CXR: Chest X-ray; mWRDs: molecular WHO-recommended rapid diagnostic tests; CRP: C Reactive Protein

Source: World Health Organisation [167]

There is a lack of evidence to inform the optimal application of these tools and the frequency or duration of systematic screening to achieve sustained epidemiological impact and therefore there are no specific recommendations in WHO guidelines. However, it is clear from studies to date that to have an epidemiological impact, a single round of screening will not suffice, and sustained interventions will be required.[174,175]

2.2.2 Community-wide TB screening

Rationale

Community-wide screening represents the broadest approach to systematic TB screening, aiming to detect undiagnosed TB in entire populations or geographic areas rather than focusing on specific risk groups. This approach is based on the recognition that in high-burden settings, substantial numbers of people with TB may not be captured through facility-based passive case finding or targeted screening of high-risk groups alone. It has been estimated that in high TB burden settings, the majority (70-90%

population attributable fraction) of TB transmission occurs in the community where social mixing occurs, rather than through household exposure. [176–179]

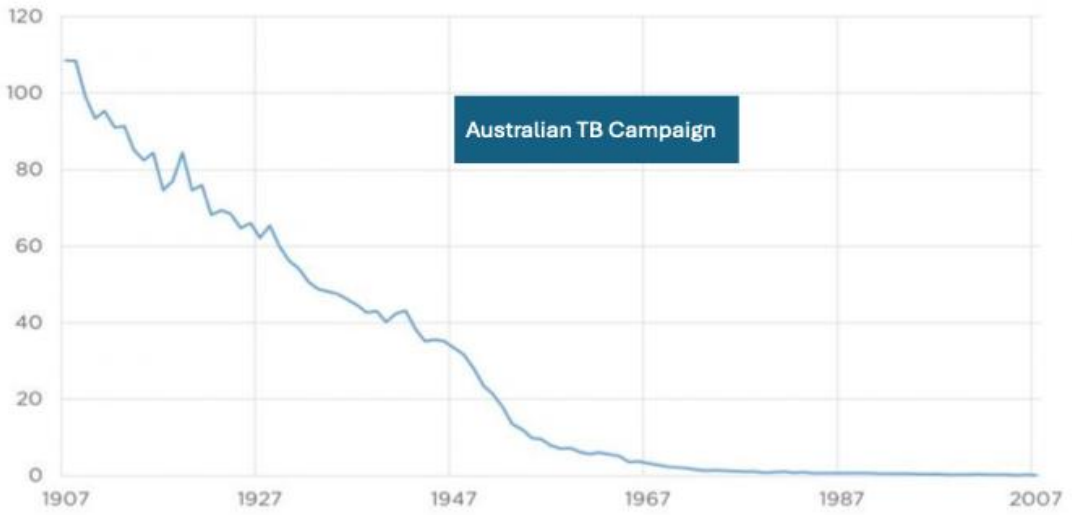
Further, community-wide screening can identify people with subclinical or asymptomatic TB who might otherwise remain undiagnosed by symptom-based passive case finding and yet may contribute to transmission.[180–184] The contribution of subclinical or asymptomatic TB to sustained TB transmission is an emerging area and research priority.[13,185] Systematic screening conducted through TB prevalence surveys have clearly shown that between 36.1% and 79.7% (median, 50.4%) of bacteriologically confirmed TB was subclinical and that CXR detected 89% (range, 73%–98%) of all bacteriologically confirmed TB.[162,186] There is increasing evidence that people with asymptomatic TB may contribute to TB transmission. An analysis that linked TBI and TB prevalence data amongst household contacts from four found that subclinical TB is similarly infectious per unit time as clinical TB and likely accounts for a large portion of global transmission (median 58%, 20–88% prediction interval).[161] A recent study that used bioaerosol sampling in 89 randomly recruited community members in South Africa detected exhaled *M. tuberculosis* among 80%, with persistence over time and levels similar to TB patients, suggesting a substantial undetected reservoir potentially driving transmission.[187]

The rationale for community-wide screening is strongest in settings with high TB burden, limited healthcare access, and evidence of substantial community transmission. In such contexts, the general population may include significant numbers of people with undiagnosed TB who do not seek healthcare spontaneously or belong to clearly defined risk groups, including contacts. Community-wide screening aims to reach these individuals through systematic, population-based approaches that bring screening services directly to communities.

Historical policy and approaches

Community-based TB screening campaigns using CXR, smear microscopy and effective treatment of active disease were widely deployed throughout the 1940s to 1970s to dramatically reduce the TB burden in HICs in North America, Europe and Australia, which at that time had moderate to high TB burden.[188–190] The Australian Tuberculosis Campaign (1948-76) provided free CXR screening, treatment and medical care and an Allowance for people undertaking treatment and was associated with substantial declines in death rate from TB over this time period (see Figure 2.3).[191,192]

Figure 2.3 Age-standardised death rate from TB (per 100,000 population) in Australia.



Adapted from the History of tuberculosis control in Australia, NHMRC [192]

In 1964, the WHO expert committee on TB recommended that community-based TB screening with mass radiography only occur if financial resources permitted, which effectively meant no resource mobilisation and implementation in LMICs and in 1974 strongly recommended discontinuation.[193,194] This was based on lower "yield" (cases detected per number screened), as TB prevalence and incidence decreased, that was similar to passive case finding.[195] The committee recommended a focus on targeted screening of higher risk groups and that resources should support passive case detection and health service strengthening.

As the global TB epidemic increased and became an emergency in the 1990s, there was an increased interest in community-based screening, in particular in settings with high HIV prevalence. However, the upfront cost was often prohibitive in LMICs. WHO recommended systematic screening beyond contacts in 2015 as a key component of its End TB strategy, with a focus on high-risk populations.[196] The rationale for this was the persistent case-detection gap, which was estimated at 3 million people with TB who were not diagnosed, leading to poor outcomes and sustained transmission driving the global TB epidemic. Secondly, evidence from an investment in prevalence surveys in multiple countries from 2007 that showed a substantial pool of undetected people with TB who were either smear microscopy negative or asymptomatic.[162,195] This was despite functional diagnostic and treatment services, as there were substantial groups of people and disadvantaged communities who could not access TB care.

Evidence of impact on TB epidemiology

High quality evidence on the impact of systematic screening or ACF is difficult obtain given the heterogeneity in TB transmission and populations in different settings and the interventions. Impact can be measured in the study population through increase in TB case notifications (or estimated incidence) or measures of impact in a broader population through the estimated incidence or prevalence of active disease (measured with a population prevalence survey) and/or serial surveys of the incidence or prevalence of TBI in children (as a measure of community transmission).[197]

Several modelling studies have shown the potential impact of community TB screening on key indicators such as mortality and prevalence. For examples, modelling of TB epidemics in China, India and South Africa predicted that ACF that increases detection by 25% will result in a 40-44% reduction in TB mortality and reduction in TB prevalence of 30-33% over 10 years.[198]

A 2021 systematic review by Burke et al. that informed the current WHO guidelines found moderate quality evidence that community TB screening (ACF, defined as any provider initiated TB detection in the community) could reduce community prevalence of TB if delivered with sufficient intensity and coverage – that is repeated rounds of screening and/or over a long period.[175] There was mixed evidence that screening increased TB case notification rates. The review synthesised data on community-based TB screening (excluding contact investigation and health care worker screening) from 36 studies from 16 countries between 1980 and 2020 and included RCTs and before-after studies.

A subsequent 2024 systematic review by van Wyk et al. applied more restrictive criteria, including only six cluster-RCTs of community-wide screening (three additional to Burke et al.) and using GRADE methodology to systematically assess evidence certainty from very low to high quality (Grading of Recommendations Assessment, Development and Evaluation).[199] This review reached consistent conclusions while clarifying that effectiveness depends critically on screening test accuracy, with mWRD screening showing moderate certainty evidence of reduced TB prevalence, while symptom screening showed only very low certainty evidence of effect.

Impact on case notifications

The impact of screening on case notifications rates was assessed in 28 studies in Burke et al., with most showing higher TB notifications in the intervention. Among four randomised controlled trials (RCTs) of screening compared to a non-screening intervention, two demonstrated increased in case notifications,[200,201] and two non-

statistically significant increases.[202,203] The studies were conducted in a variety of setting and populations - nine in high-risk settings (prisons, people with homelessness, miners, refugee camp), five in the general population and the remainder in sub-populations (remote, urban, Indigenous). There were a variety of models of care, but all were conducted in the community. Three studies tested and treated TB infection. The majority (21) used symptom screening, two used tuberculin skin test (TST) and five used CXR as the initial screening test.

Impact on population TB epidemiology

The review included data from two large cluster-RCTs conducted in Zimbabwe and South Africa (ZAMSTAR) and Vietnam (ACT-3) where the primary outcome was prevalence of bacteriologically-confirmed pulmonary TB disease in adults, and the secondary outcome was the prevalence of TBI in children.[204,205] An addition cluster-RCT in Zimbabwe and South Africa (DETECTB) compared two types of ACF on case notification and evaluated TB prevalence using a non-randomised before and after comparison.[204,206] It is notable that the Southern Africa countries have a high HIV prevalence, whereas Vietnam does not. Six other observation studies evaluated the effect of TB screening on prevalence but were assessed as having a critical risk of bias.

In DETECTB, 46 urban neighbourhood clusters were randomised to six rounds of ACF, with each round conducted at six-monthly intervals with either mobile van or door-to-door visits using symptom screening and smear microscopy (55,000 participants in each group). The before-and-after comparison of culture-confirmed TB in a sample of 12% of households showed a reduction of prevalence by 41% (risk ratio 0.59 95% CI 0.40-0.89).[206]

The ZAMSTAR study randomised 24 communities to two interventions - “enhanced case finding” (ECF, community mobilisation to present at community and health facility sputum collection points) and TB-HIV care (household or clinic; non-ECF), over 3 years. Among 65,000 participants randomly selected from the 24 communities, there was no difference in culture-confirmed TB in adults measured at year 4 comparing the ECF and non-ECF interventions (prevalence ratio of 1·09, 95% CI 0·86–1·40). Among schoolchildren serially tested with tuberculin skin test before and after the intervention period, there was also no difference in the prevalence of TBI in ECF vs non-ECF groups (prevalence ratio 1·36, 95% CI 0·59–3·14).[204]

In Vietnam, annual community wide door-to-door screening was conducted for three years in 60 clusters–sub-communes (village or suburb) with an average study population

of 1000 people. Participants aged 15 years and older in the intervention clusters were asked to provide sputum, regardless of symptoms and this was tested using Xpert MTB/RIF and compared with control clusters (passive case finding alone). A TB prevalence survey was conducted in the fourth year and showed a 44% reduction in the prevalence of microbiologically confirmed TB in the intervention group compared with the control group (prevalence ratio 0.56, 95% CI 0.40-0.78). A prespecified secondary outcome was the prevalence of TBI (using an interferon gamma release assay) among children born 1 to 2 years before the intervention commenced was not different between groups (prevalence ratio 1.29, 95% CI 0.70-2.36). However, a post-hoc analysis of children aged 3 to 10 years at the start of the intervention had a 50% lower prevalence of infection in the intervention compared with control group (prevalence ratio 0.5, 95% CI 0.32-0.78).[205] The incidence rate of TB in the study population was shown to have a statistically significant decrease across three annual cohorts and by 57% from baseline.[207] Van Wyk et al. classified this Vietnam study as providing the highest quality evidence in their systematic review, noting that mWRD screening probably reduces TB prevalence with moderate certainty evidence - the only intervention to achieve this level of evidence quality in their GRADE assessment.[199]

Since the systematic review by Burke et al. that informed the current WHO guidelines there has been no additional RCT conducted to evaluate community TB screening on incidence, prevalence or transmission - COVID-19 disruptions were a factor. There have been two cluster-RCTS that evaluated the effect of systematic screening on TB case notification (conducted in Malawi and South Africa) that have demonstrated benefit[208,209] and one with no benefit (Malawi).[210] Since 2021, three large cross-sectional TB prevalence surveys that evaluated systematic screening interventions and a cluster-RCT have been published.

First, the TREATS study, which was a TB prevalence survey conducted as a follow-up to the PopART cluster-RCT (HPTN 071) conducted in the same communities as ZAMSTAR.[211,212] The PopART intervention involved 1 million participants and randomised 14 communities to two combination HIV prevention arms – one universal ART initiation and the other by local guidelines - and 7 communities to standard of care over 4 years (2014-17). The intervention included systematic symptom screening for TB at the household level with Xpert MTB/RIF for diagnosis. The TREATS study was a TB prevalence survey of a sample of 50,000 participants conducted from 2019-21 using CXR with computer-aided detection (CAD) and symptoms. There was no difference in TB prevalence across the groups (prevalence ratio 1.14 95% CI 0.67-1.95 p=0.60) and

overall TB prevalence was 0.92%. Similarly, a TBI survey of adolescents and young adults (15-24 years) enrolled in 2018-19 and followed up at 12 and 24 months, showed no evidence of reduced transmission (incidence-rate-ratio 1.45, 95% CI 0.97-2.15 p=0.063).

Second, a concurrent adult pulmonary TB and child TBI prevalence survey was conducted in Karachi, Pakistan in 2018-19 following a large community TB screening initiative over the proceeding seven years.[213] The survey compared districts with prior ACF those with no prior ACF with a total of 35,000 adolescents and adults ≥15 years and 1,500 young children (2-4 years) participating in the disease and infection surveys, respectively. While, not statistically significant, there was a trend to lower prevalence and annual risk of TB infection in the prior ACF, compared with no prior ACF zones.

Third, Kendall et al. performed two intensive TB screening campaigns in Kampala, Uganda in 2019 and 2021, using Xpert Ultra irrespective of symptoms. They observed a 45% (25-60%) lower TB prevalence in the second campaign compared to the first. Despite COVID disruptions, TB care seeking continued and the authors concluded the decline was likely multi-factorial.[214]

Impact on outcomes, economic evaluation and community perspectives

There have been five other relevant systematic reviews of systematic screening for TB but with different scope. Bohlbro et al., also published in 2021, reviewed 197 studies to assess the effect of screening on case notifications in the general population and high risk groups (including contacts) and found high yields.[215] Telisinghe et al. conducted a systematic review of TB screening on individual outcomes (bacteriological, pre-treatment loss to follow up, treatment success, mortality and costs) found limited data which was difficult to compare and interpret.[216] Feasey et al. assessed the indirect impact of community TB screening on routine TB case notification and found weak mixed evidence of its effectiveness.[217] Alsdurf et al. conducted a systematic review of economic evaluations of TB screening targeting high-risk groups.[218] Analysis of 27 studies showed that screening is likely to be cost-effective in a high TB prevalence population. A qualitative evidence synthesis (systematic review) on community perspectives of TB screening and contact investigation found that people need to navigate a complex cascade of care, face significant structural barriers (access, out of pocket costs, stigma and discrimination) and this operates in health systems that are under strain.[219]

Policy and implementation considerations

The weight of evidence demonstrates that systematic screening for TB increases case detection and can reduce TB prevalence and transmission if delivered with sufficient intensity and coverage, supporting WHO guidelines. However, the success depends on the local epidemiology, context (including health system, individual and community factors) and the intervention. While WHO recommends a range of screening modalities, the evidence supports the use of more sensitive screening approaches such as mWRDs, over the symptom-based approaches that dominate many current programes.[199] This is logical, given the contribution of asymptomatic TB to transmission. The use of CXR screening which can detect asymptomatic TB, including with digital CAD, is increasing, despite the absence of a high-quality intervention study, but its use is limited by feasibility.[220–223] Designing appropriate studies to assess the impact of TB screening is complex and comparison between studies and TB epidemics that have significant heterogeneity is difficult.

Most importantly, the ACT3 study demonstrates that it is possible to dramatically reduce TB transmission with systematic screening. The effect seen equates to a 15% annual decline in TB prevalence with screening and a number needed to screen of 1,002 to prevent one case of TB. There were some key differences in ACT3, compared to the other studies which showed no effect (ZAMSTAR, TREATS) or a small effect (DETECTB) of screening on TB prevalence. First, there were differences in HIV prevalence between Vietnam (0.3%) and Southern Africa (7-20%).[224] A co-existing HIV epidemic is a strong driver of community TB transmission and therefore interventions with greater effectiveness are required.[117] Second, ACT3 implemented the most intense intervention compared to the other studies with universal screening of spontaneously expectorated sputum (vs symptom screening), a more sensitive test (Xpert MTB/RIF vs sputum microscopy), high population coverage (>60%) and multiple annual screening rounds (PopART also had annual screening). Third, there may have been key structural determinants as to why transmission reduction in Vietnam was more feasible than the Southern African countries including lower baseline TB prevalence, greater health system capacity, lower socio-economic vulnerability and the presence of a more functional TB program.

2.2.3 Contact investigation

Rationale

The rationale for contact investigation is based on the well-established principle that contacts of TB patients have substantially higher risk of both TB infection and disease compared to the general population.[114,167,225] Factors that influence this risk include infectiousness of the index case (including the duration and extent of exposure), environmental factors (ventilation) and host susceptibility.[171,226] Following exposure, contacts have a high risk of developing TBI and disease, in particular young children(<5 years) and PLHIV and therefore is an opportunity to provide TPT.[9,51,52] The highest risk of TB disease occurs in the first two years following exposure.[52,164,227]

Historical policy and approaches

Contact investigation is a cornerstone of outbreak management and disease control strategies.[228] It has been implemented in HICs since pioneered by the New York City TB program in the early twentieth century.[229] Through the 1950s and 1960s vertical TB control programs were established in HICs that focussed on population screening and case management.[82] Screening of contacts would occur within the mass screening programs.[230] As the benefit of isoniazid preventive treatment (IPT) was established, child contact investigation was implemented through paediatric units, and mainly in HICs, mostly as a passive, centralised approach.[231,232] From the late 1960s and 1970s, the WHO recommended TB model of care changed to integrated service delivery through primary care following Medical Research Council (UK) studies in India.[40,82,233] This led to the dismantling of systematic screening and IPT, including contact management. The 1974 WHO Expert Committee on TB considered case-finding in contacts (particularly those who were symptomatic) would offer significant yield, however a well performing health service would “attract symptomatic cases.”

This approach continued into the DOTS strategy era, where the WHO discouraged contact investigation in LMICs, in lieu of a focus on passive case finding, diagnosis and treatment when resources are limited.[193,234] As part of the 2006 Stop TB strategy, WHO developed child TB guidelines which recommended contact investigation and the provision of TPT on the basis of symptom screen alone for young children who were contacts of index smear-positive pulmonary TB cases, encouraging implementation in LMICs.[84,235] Despite this, implementation of contact investigation in LMICs was and remains limited.[236]

In 2012, the WHO shifted course to strongly recommend systematic screening of contacts in high-TB burden countries (LMICs) due to evidence of the high yield in multiple settings, the individual benefits of early detection and potential for reducing transmission, including MDR/RR-TB.[116,237] Subsequent guideline updates have expanded the scope of recommendations, incorporating new evidence on optimal screening tools, the role of TPT, and implementation considerations across different epidemiological contexts.[196] The 2021 WHO guidelines reaffirm that household contacts and other close contacts of individuals with TB disease should be systematically screened for TB, representing the highest priority group for screening activities.[167]

Impact on TB epidemiology

The most recent systematic review of contact investigation (Velen et al.) conducted for the 2021 WHO guidelines evaluated observational and randomised studies from 2011-19 and found the pooled prevalence of TB disease among contacts 3.6% (95% CI: 3.3–4.0) and incidence in the first year following exposure was 2.0% (95% CI 1.1-3.3), dropping to 0.5% at 5 years.[238] The pooled prevalence of TBI among contacts was 42.4% (95% CI 38.5–46.4%; I^2 =99.8%,). Contact investigation increased TB case notification (relative risk [RR] 2.5, 95% CI 2.0–3.2) and TB case detection (OR 1.34, 95% CI 0.43–4.24) and decreased mortality (RR 0.6, 95% CI 0.4–0.8) and population TB prevalence (not statistically significant - RR 0.82, 95% CI 0.64–1.04). Pooled prevalence varied according to diagnostic strategy and was higher with mWRDs compared to symptom screening, CXR or microscopy.

The pooled prevalence of TB disease among contacts in high-TB burden countries was 5.0% compared with 1.9% in low TB burden countries. This is likely due to multiple factors, including increased vulnerability within households from factors such as overcrowding, malnutrition, HIV, indoor air pollution, as well as higher risk from transmission occurring outside the household in high burden settings.[178,239,240] A separate systematic review of the yield of contact investigation in LMICs included 95 studies and showed a pooled yield of 2.87% (2.6–3.1, I^2 97.8%) and TBI of 43.83% (38.1-49.6% I^2 99.36).[241] A 15-year cohort study of 420,00 household contacts in Brazil showed that the TB incidence was 16 times higher in contacts than the general population, and the highest risk (62 times) in child contacts under 5 years.[242]

The 2021 Velen et al. systematic review included three RCTs[204,243,244] on the effectiveness of contact investigation compared with passive case finding on TB detection with a further four RCTs[245–248] published since. These are summarised in Table 2.3**.** The ZAMSTAR study was the only RCT of contact investigation to assess a

population level epidemiological outcome.[204] It evaluated a complex intervention that included household TB contact investigation and showed that TB prevalence was reduced by 18%, but this was not statistically significant, nor was the reduction in TBI.

An important cluster-RCT of household contacts investigation (ACT2) that compared to passive case finding in Vietnam showed a 2.5-fold increase (RR 2.5; 95% CI: 2.0–3.2) in the cumulative incidence of TB notification of contacts over 2 years. Contacts of all ages were invited to district clinics every 6 months for symptom screen, clinical assessment and CXR for 2 years. In a post-hoc analysis, there was a 40% reduction in all-cause mortality among household contacts (RR: 0.6; 95% CI: 0.4–0.8).[244] A stepped-wedged cluster-RCT in Peru found that active case finding among household contacts detected significantly more TB cases than passive case finding (199.29 vs 132.13 per 10,000 contacts/year, IRR 1.51), but was not cost-effective.[246]

Four RCTs showed no significant effect size, when compared to standard of care.[243,245,247,249] The largest of these in South Africa found that household contact tracing with intensive screening did not reduce incident TB or death at 15 months compared to standard care (2.9% vs 3.1% cumulative incidence, HR 0.90).[245]

Policy and Implementation considerations

While contact investigation as the only modality of systematic screening will be insufficient to achieve the goal of ending TB, it has a critical role in improving case detection and improving outcomes by offering treatment for TB and TBI.[250] Despite sub-optimal implementation in high TB burden countries, it should be routine in all TB programs, as it is in low TB burden countries.

The WHO 2021 guidelines state that contact investigation should always be done for specific index cases who have higher prevalence of TB (shown as weighted pooled prevalence in the systematic review):[238]

- bacteriologically confirmed pulmonary TB (3.4% (95% CI: 2.9-3.8))
- bacteriologically confirmed or clinically diagnosed MDR/RR-TB (3.7% (95% CI: 2.4-5.3))
- PLHIV (11.6% (95% CI: 8.2-15.4))
- Children under 5 years (3.9% (95% CI: 2.5-5.4))

The definition of a household or close contact can be operationally defined, in particularly in settings where household structures are complex. The standard WHO definitions are:

- Household contact: person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index patient during the 3 months before the start of current treatment.
- Close contact: A person who does not live in the household but who shared an enclosed space, such as a social gathering place, workplace or facility, with the index patient for extended periods during the day during the 3 months before the current disease episode commenced.

Table 2.3 Summary of randomised controlled trials for contact investigation effectiveness

Author (year) and Country	Study population & setting	Design: Intervention vs Control	Primary outcome	Secondary outcomes	Results	Evidence for impact and comments
Ayles (2013) Zambia, South Africa ZAMSTAR	24 communities (~1.2 million population), Rural and urban	cRCT community 2x2 factorial Enhanced case finding (ECF) and/or household intervention vs standard care	TB prevalence in communities	TB infection incidence in children	No statistically significant reduction in TB prevalence; Household intervention showed 18% reduction in TB prevalence (p<0.064)	Moderate evidence: Not significant, but underpowered. Two independent indicators of burden provide some evidence of a reduction in TB among communities receiving the household intervention
Fox (2018) Vietnam ACT2	25,707 household contacts of 10,964 TB index patients Rural and urban	cRCT district Active household contact investigation vs passive case finding	Cumulative incidence of registered TB cases among contacts over 2 years	Smear-positive TB, treatment outcomes	Intervention: 1788 vs Control: 703 per 100,000 contacts (RR 2.5, 95% CI 2.0-3.2, p<0.001); Smear-positive RR 6.4 (95% CI 4.5-9.0)	Strong: Significant improvement in case detection with active screening
Davis (2019) Uganda	919 household contacts of 372 TB index patients in Urban Kampala	cRCT household Home-based SMS-facilitated evaluation vs clinic referral	TB evaluation completion within 14 days	TB and HIV diagnoses and treatments	Completion: 14% vs 15% (difference -1%, 95% CI -9% to 7%, p=0.81); TB yield: 1.5% vs 1.1% (p=0.62)	None: No improvement in process outcomes with home-based approach. No epidemiological impact assessed
Hanrahan (2019) South Africa Kharitode	3,755 TB patients across 56 clinics in rural Limpopo	cRCT clinic Contact tracing (household/incentive-based) vs facility-based screening	Number of TB patients started on treatment per clinic	Contact screening yield	Treatment initiation ratio: 1.04 (95% CI 0.83-1.30, p=0.73); Contact tracing yield: 12/1,677 contacts (0.7%)	None: No improvement in process outcomes with home-based approach. No epidemiological impact assessed. Excluded from Velen et al systematic review

Author (year) and Country	Study population & setting	Design: Intervention vs Control	Primary outcome	Secondary outcomes	Results	Evidence for impact and comments
Shah (2020) Peru	12,566 household contacts of 3,222 TB index cases in urban Lima	Step wedged cRCT health facility Active case finding by NTP providers vs passive case finding	TB incidence rate ratio among household contacts	Incremental cost-effectiveness ratio	ACF: 199.29 vs PCF: 132.13 per 10,000 contacts/year (IRR 1.51, 95% CI 1.21-1.88)	Strong: Significant increase in case detection but not cost-effective
Hirsch-Moverman (2021) Lesotho PREVENT	973 adult TB patients and their child contacts	cRCT health facility Community-based intervention vs standard care	Child contacts identified and screened per adult TB patient	Not detailed	Contact yield: 0.40 vs 0.20 per TB case (p=0.08); Screening: 94% vs 62% (p=0.13)	Minimal: Marginally higher yield, not statistically significant
Martinson (2021) South Africa	8,588 household contacts of 2,062 TB index patients in 2 rural provinces	cRCT household Home tracing with intensive screening vs clinic referral letters	Incident TB or death at 15 months	TST positivity in children, undiagnosed HIV	Incident TB/death: 2.9% vs 3.1% (HR 0.90, 95% CI 0.66-1.24); Prevalent TB: 3.2% detected in intervention arm	None: No reduction in incident TB despite intensive screening

cRCT: cluster randomised controlled trial; ECF: enhanced case finding; RR: rate ratio; SMS: short message service; ACF: active case finding; PCF: passive case finding; NTP: National Tuberculosis Program; IRR: incidence rate ratio; HR: hazard ratio

The 3-month period is arbitrarily defined to capture the infectious period of TB. Eligibility for TPT should be assessed among all TB contacts who are screened and found not to have TB disease. This is particularly important in young children who have high risk of progression to active TB following infection, with active TB developing within 3 months of exposure in the majority.[52]

The standard model of care for contact investigation has historically been facility-based with contacts required to attend health services for evaluation, particularly in HICs. Decentralised models that involve household-based evaluation have been increasingly implemented in high TB burden LMICs demonstrating higher uptake, better outcomes and improved acceptability and feasibility.[251–254]

Collectively, this review demonstrates that there is good evidence to support systematic screening for TB. However, critical evidence and implementation gaps persist in determining the optimal settings and populations to screen, the optimal screening algorithms, and operational models. Nguyen, Marks and colleagues argue that while the higher risk groups have higher TB incidence, in high-burden settings, TB in the general population drives the epidemic and therefore should be the focus of systematic screening for active TB.[100,255] On the other hand, others such as Ortiz-Brizuela and Menzies make a case for strengthening local health system capacity to diagnose TB and focus on systematic screening of household contacts.[256]

2.3 TB preventive treatment

2.3.1 Rationale

TB preventive treatment (TPT) is one of the key interventions recommended by WHO to achieve the End TB targets.[27] It is estimated that of 1.7 billion people globally who have had TBI, approximately 5-10% will develop active TB disease during their lifetime, with the highest risk in the first two years.[14,78,79] These estimates are based on immunoreactivity to TB. A major limitation is that there is no test for diagnosis of TBI or for predicting those at greatest risk for progression to active disease. More recent modelling that considers self-clearance of infection substantially lowers the estimated number of people with viable TBI who would benefit from TPT (by 27-56%). This model by Emery et al. estimates self-clearance to be 24.4% (17.8–32.6%, 95% UI) of individuals within 10 years of infection, and 73.1% (64.6–81.7%, 95% UI) over a lifetime.[78] "People with a positive test for infection have a higher risk of developing TB, with substantially elevated risk in specific groups: household contacts (4.8% cumulative incidence at 5

years; 15.6% in children under 5 years), PLHIV (10%), and other immunocompromised individuals (4.8%).[52,257,258] Therefore, current approaches recommended by the WHO focus on detection and treating TBI in those at highest risk of progressing to active TB.

By treating TB infection before progression to active disease, TPT (1) prevents TB disease in individuals and (2) prevents potential onward transmission of TB from that individual to others. Preventive treatment or chemoprophylaxis has been used in other infectious diseases as pre-exposure prophylaxis (HIV, malaria for at risk groups) or post-exposure prophylaxis / outbreak control (HIV, leprosy, meningococcal disease, pertussis, Group A Streptococcus). In TB, TPT is used as post-exposure treatment, with or without a test for infection – tuberculin skin test (TST) or interferon gamma release assay (IGRA).

It is well established through clinical trials of isoniazid that TPT can reduce the development of active TB by 60-90% in non-HIV infected at risk groups. [259,260] Martinez et al. conducted a systematic review and individual participant data meta-analysis of contact tracing studies (32 studies with 430,000 individuals) and found the overall effectiveness of 49% (aHR 0.51(95% CI 0.44-0.60)) in reducing TB incidence.[261] Effectiveness among people with a positive test for TBI was 83% (similar across all age groups), 53% for young children <5 years with a negative test, 54% among PLHIV, and 69% in high burden settings.

At the population level, mathematical modelling consistently demonstrates that TPT can achieve substantial impact when implemented at scale and combined with systematic screening and treatment, as a comprehensive detect-treat-prevent approach.[250,262–264] A recent WHO modelling study and investment case for four countries (Brazil, Georgia, Kenya, and South Africa) showed that TB screening plus TPT in target groups (contacts, PLHIV, other priority populations) could achieve 29-54% reductions in TB incidence by 2050 and 23-52% reductions in TB deaths.[265] This comprehensive approach was cost-saving with a societal return on investment ranging from 4:1 to 39:1 for every dollar.

2.3.2 Historical policy and approaches

Isoniazid was introduced for the treatment of active TB in the 1950s and was soon used in a series of six clinical trials to evaluate the effectiveness of TPT led by Comstock and Ferebee for the US Public Service.[266–268] This included a landmark community-based cluster-RCT of isoniazid preventive treatment (IPT) for all household contacts in Bethel, Alaska that demonstrated a 69% reduction in TB incidence after 1 year with a durable

effect to 19 years.[266,269] Similar studies were conducted in Greenland, Tunisia, Japan, Kenya and France.[270–274] Following this, the American Thoracic Society guidelines recommended IPT for people with a positive TST and no active TB in 1965.[275]

However, the WHO Expert Committee on TB in 1964 was much more circumspect on their recommendations, consistent with the focus on passive case finding and prioritising diagnosis and treatment at health services.[193] In 1974 the WHO abandoned TPT and re-iterated this again in 1982 in joint report with The International Union Against Tuberculosis, while recommending and conducting research on different IPT regimen durations.[194,276,277]

> Summing up, the Committee felt that, at the present stage of knowledge, it could not recommend secondary chemoprophylaxis for mass application but only for individuals and groups at special risk. Even this application was justifiable only in a programme that had achieved a high degree of perfection in its case-finding and treatment activities.

WHO Expert Committee on TB, 1964[193]

4.2.13 *Preventive treatment*

> The Committee emphasized that a policy of preventive treatment (often termed chemoprophylaxis) is irrational, even for special risk groups, unless the treatment programme for patients suffering from infectious tuberculosis is widespread and well organized, and achieves a high rate of cure.
>
> Although isoniazid can be considered a safe drug in the treatment of frank tuberculosis, its side effects must be viewed in a completely different light when it is administered to persons who have only a small chance of deriving benefit. In chemoprophylaxis programmes, cases of isoniazid-associated hepatitis are reported in increasing numbers, and some have proved fatal.
>
> The benefits must be weighed against not only the side effects but also the inconvenience to the individual, including the social and economic penalties of being labelled " high risk " or " tuberculous ". Furthermore, the difficulty of persuading apparently healthy individuals to accept long-term medication, and the substantial cost (manpower and other resources) must also be taken into consideration.
>
> For these reasons, the Committee considered that preventive treatment was not suitable for mass application in a community health programme.

WHO Expert Committee on TB, 1974[194]

> Although the most logical use for preventive treatment (chemoprophylaxis) would be in easily identified, young, infected contacts of newly diagnosed infectious cases, in practice it has virtually no role in developing countries. This is because preventive treatment cannot be an appropriate component of a tuberculosis control programme unless resources can be allocated to it without compromising the ability of the programme to provide curative treatment to virtually all tuberculosis cases. There is a need for research in preventive treatment to determine if potent new drug combinations given to selected tuberculin-positive individuals for very short periods of time is effective and can help to improve the epidemiological situation.

WHO and The International Union Against Tuberculosis, 1982[276]

The policy and implementation barriers to adopting TPT in high TB burden settings were primarily focused on perceived effectiveness, feasibility and cost, where the priority and potential for greater impact was considered to be from strengthening passive case detection and treatment approaches.[193,194,278] In addition, there were also conceptual barriers and concerns from clinical and public health policy makers on treating healthy individuals with potentially toxic medications, and concerns around generating resistance.[130,279,280] Importantly, there were different (WHO and national) recommendations for HICs (which had lower TB burden) and LMICs, where the TB epidemic was uncontrolled.

The programmatic strategy of TPT remained largely abandoned until the HIV epidemic. In 1989 the WHO and International Union Against Tuberculosis and Lung Disease prioritised research into the effectiveness of IPT, catalysing resource mobilisation and also the re-prioritisation of TPT for young child contacts.[281] Nicholson et al. in an analysis of global MDR-TB treatment policy argue that the rationale of cost and feasibility over evidence for benefit represents a double standard for TB care; whereas WHO guidelines should establish universal evidence-based recommendations, with countries then adapting implementation strategies based on local epidemiological context, resources, and feasibility.[282] A similar case can be made for TPT policy, which only aligned on a single standard of care for HICs and LMICs in 2018 WHO guidelines, while acknowledging the need for local decisions based on epidemiology, resources and feasibility.[283]

2.3.3 Current WHO guidance

The current WHO guidelines for TPT were published in 2024.[9] As the studies on contact investigation and TPT in this thesis were conducted from 2017 to 2022, WHO guidelines over this period have been reviewed. Table 2.4 shows the evolution of WHO guidelines for TBI and TPT since the DOTs era to the present (2024). [9,115,116,159,234,235,283,284] WHO has progressively widened eligibility recommendations for TPT since the first specific guidance on the treatment of TBI in 2015, with current guidelines emphasising its role as an essential component of comprehensive TB control strategies. In 2018, based on an updated systematic review, a conditional recommendation was made to consider TPT in household contacts of all ages and based on observational studies, consider TPT contacts of MDR-TB index cases following an individualised risk assessment.[283] The 2020 WHO consolidated guidelines on TB prevention provide strong recommendations for TPT provision to household contacts, people living with HIV, and other high-risk populations, recognising TPT as equally important to treatment of active disease for achieving long-term transmission reduction.

The 2024 update integrated screening recommendations, updated with newer tests for screening and TBI and made a new recommendation for TPT with 6 months of levofloxacin (6Lfx) in contacts exposed to MDR/RR-TB, as displayed in Table 2.4. While WHO leaves open the option for screening tests including CXR or mWRD to exclude active TB prior to TPT initiation, it recommends that CXR is not a requirement for TPT initiation in asymptomatic child contacts under 5 years or PLHIV.[285–287] CAD software for interpreting CXR is an important innovation that reduces the need for expert readers, however is only validated in adolescents over 15 years and adults.[221,286,288]

The WHO noted that all household contacts were at substantially greater risk of progression to active TB than the general population regardless of their age or TBI status, and that while young child household contacts were at the greatest risk of progression to active TB, the prevalence of TBI was highest among adolescents over 15 years and adults. This led to the strong recommendation for TPT in young child contacts after the exclusion of active TB on screening. To improve implementation and increase access, a CXR to screen for active disease and a positive test for infection were not considered as necessary to initiate TPT. This approach has been shown to be effective and safe.[289] For all other ages, WHO conditionally recommends TPT- on the balance of individual benefit and harm and the population risk of ongoing TB transmission (considering local epidemiology). A test for TBI is desirable prior to provision of TPT in

older children (5 years and over), adolescents and adults. These recommendations are regardless of HIV status.

Table 2.4 Evolution of WHO TB preventive treatment guidelines and recommendations

Year	Guideline	Target Populations Eligible for TPT *(as changes from previous guideline)*
1993	DOTS: No specific document	
1999	What is DOTS	PLHIV
2006	Stop TB strategy: No specific document	
2009	Implementing the Stop TB Strategy Guidelines for NTPs on the management of TB in Children	PLHIV Recent TST converters Young child contacts (<5 years)
2011	Guidelines of TB case-finding and IPT in PLHIV	PLHIV in resource-constrained settings
2012	Recommendations for investigation contacts in LMICs	PLHIV and children <5 years who are contacts The value of providing treatment for TBI in LMICs is not proven and not recommended as a broad program approach
2015	Guidelines on the management of LTBI	Low TB incidence countries: PLHIV, contacts, immunosuppressed (anti-TNF, dialysis, transplant, silicosis) *Conditional* - prisoners, health workers, immigrants High TB incidence countries: PLHIV, child contacts *Not recommended:* MDR-TB contacts
2018	LTBI: Updated and consolidated guidelines for programmatic management	As above plus High TB incidence: *Conditional*- Household contacts (all ages) *Conditional:* selected MDR-TB contacts with individualised risk assessment
2020	Consolidated guidelines: module 1	Single standard for all settings: PLHIV, household contacts, other risk groups *Not recommended:* diabetes, harmful alcohol use, smokers, underweight
2024	Consolidated guidelines: module 1 (version 2)	Contacts of MDR/RR-TB Removed recommendations against diabetes, harmful alcohol use, smokers, underweight

DOTS: directly observed treatment, short-course; IPT: isoniazid preventive treatment; LMICs: low- and middle-income countries; LTBI: latent TB infection; MDR/RR-TB: multidrug-resistant/rifampicin-resistant TB; NTP: national TB program; PLHIV: people living with HIV; TBI: TB infection; TNF: tumour necrosis factor; TPT: TB preventive treatment; TST: tuberculin skin test

Source: World Health Organisation [9,115,116,159,234,235,283,284]

Table 2.5 WHO guidelines for TB preventive treatment (2024)

Population	Eligibility and age group	Testing for TB Infection
People with HIV	Infants <12 months who are contacts	Not required
	Children ≥12 months who live in a high TB transmission setting, adolescents and adults (including pregnant women, people on antiretroviral treatment and those who have completed TB treatment)	Recommended (but not required)
Household contacts of bacteriologically confirmed pulmonary TB	Children <5 years	Not required
	Children ≥5, adolescents and adults	Recommended (but not required)
	MDR/RR-TB	Recommended (but not required)
Immunosuppressed people	Anti-TNF factor treatment, dialysis, transplantation, silicosis	Recommended - systematic testing
Priority sub-populations	Prisoners, health workers, immigrants from countries with high TB burden, homeless people, people who use drugs	Consider systematic testing

MDR/RR-TB: multidrug-resistant/rifampicin-resistant TB; TNF: tumour necrosis factor

Source: World Health Organisation[9,290]

2.3.4 Tests for TB infection

Testing for TBI is generally recommended where available as it will target TPT to those who will benefit most. However, testing for TBI is not required to initiate TPT in young children or PLHIV. Either a tuberculin skin test (TST), or interferon-gamma release assay (IGRA) can be used to test for TBI and are considered equivalent with different implementation considerations for each (feasibility, cost, acceptance).[291] In 2024, WHO made a conditional recommendation to support the newer *M. tuberculosis* antigen-based skin test (TBST). As all tests measure immunoreactivity to *M. tuberculosis* antigens and conversion to positive following infection occurs within 8 to 12 weeks.

The intradermally administered TST was first developed by Mantoux in 1912 and standardised and produced at scale in the 1960s.[292] Its use declined as population wide screening and contact investigation in high burden countries was scaled back in the DOTS and Stop TB eras. The test measures delayed-type hypersensitivity responses to intradermally administered purified protein derivative that contains killed mycobacterial

antigens derived from *M. tuberculosis*, *M. bovis*, BCG, and non-tuberculous mycobacteria (NTM). Interpretation thresholds vary by population risk: induration ≥10 mm indicates positivity in immunocompetent HIV-negative individuals, while a reduced 5mm cut-off applies to people living with HIV and other immunocompromised populations. The sensitivity from a meta-analysis was 77% and specificity 62%.[293] False-positive results occur in BCG-vaccinated individuals and those with NTM exposure. Conversely, false-negative results are common among immunosuppressed patients who fail to mount adequate immune responses. Operational challenges with TST implementation include the requirement for two visits – initial placement and reading 48 to 72 hours later, training for placement and interpretation and the need for cold chain. There is also now only a limited number of global manufactures, resulting in global supply issues.[294]

Interferon-gamma release assays (IGRAs) represent a blood-based alternative measuring T-cell IFN-γ production following stimulation with specific *M. tuberculosis* antigens (ESAT-6 and CFP-10) and therefore offering improved specificity over TST due to reduced false positives from BCG or NTMs.[292] However, IGRA requires more specialised laboratory equipment to centrifuge, incubate and analyse blood samples, which often precludes its use in LMICs. The sensitivity from a meta-analysis was 73% and specificity 74%, although other studies from low burden settings report a much higher specificity (>98%).[293]

Newer *M. tuberculosis* antigen-based skin tests (TBSTs) were WHO endorsed in 2022 and administer the *M. tuberculosis*-specific antigens used in IGRA, intradermally. The clinical trials and emerging evidence suggest the TBSTs may have similar sensitivity to IGRAs and may have better performance in children, adolescents and in PLHIV, however further studies are needed.[292,295]

2.3.5 Regimens for TPT

Current WHO-recommended TPT regimens include 6 to 9 months of daily isoniazid (6H, 9H), 3-month weekly isoniazid-rifapentine (3HP), 3-month daily isoniazid-rifampicin (3HR), 4-month daily rifampicin (4R) and 1-month daily isoniazid-rifapentine (1HP) for TBI presumed to be drug-susceptible. The 6-9H, 3HP and 3HR regimens are strongly recommended, with others a conditional recommendation. All regimens can be used irrespective of HIV status. In 2024, the WHO recommended 6-months of daily levofloxacin (6Lfx) for contacts of MDR/RR-TB based on the results of two clinical trials.[125]

The decision on which regimen to use should consider country guidelines, availability including child-friendly formulations, age, clinical factors - risk of toxicity or interaction, co-morbidity, resistance profile of the index cased and the individual's preferences. Fixed dose combinations and child-friendly dispersible formulations are available for 3HR and 3HP (dispersible formulation is not a FDC) which have demonstrated better tolerability and completion rates.[296,297]

Evidence for effectiveness of TPT

There is a strong evidence base for the effectiveness of TPT at the individual level, based on RCTs that initially compared isoniazid with placebo and as a result 6H has been the standard of care for decades in many settings (9H has been limited by lower completion rate).[259,260,298,299] The TEMPRANO study, published in 2015 showed the additional benefit of IPT to ART in PLHIV in reducing TB and severe illness.[300] The study also demonstrated that TPT had a significant impact on mortality, independent of the effect of ART.[301] A meta-analysis of this trial and two other RCTs convincingly demonstrated that IPT reduced the risk of TB in PLHIV, making ART with TPT standard of care in high TB incidence settings for PLHIV.[283,302]

In the early 2000s, multiple large rigorous large clinical trials established the non-inferiority and safety of the rifamycin-based regimens against isoniazid monotherapy[303–309] This has been further validated by meta-analyses demonstrating comparable efficacy and completion rates in.[261,310–313] The outcomes assessed were the incidence of active TB in the study population, along with measures of completion and safety (adverse events).

The 3HP regimen showed higher completion rates across all subgroups (adults with HIV: RR 1.25, adults without HIV: RR 1.19, children/adolescents: RR 1.09) and significantly lower hepatotoxicity risk (RR 0.26 in HIV-positive, RR 0.16 in HIV-negative adults).[303–306] Similarly, 4R demonstrated 15.1% higher completion rates versus 9H in adults, with 13.4% improvement in children.[307,308,314] The 3HR regimen has been show in children to be as safe and superior to 9H in a larger RCT.[315] The evidence base for 3HR in adults is less well developed, however a meta-analysis of smaller RCTs and several observational studies that demonstrate its equivalent effectiveness to isoniazid with better compliance and less adverse events.[315–317]

Safety of TPT

The safety of TPT is an important requirement if the intervention is to be scaled in terms of major drug adverse effects (which would influence a decision to prescribe or accept)

but also minor effects that would influence the regimen tolerability and completion. The adverse effect of isoniazid-induced hepatotoxicity is an issue (rates of 0.36%) that can progress to the rare but serious complication of acute liver injury that can potentially lead to fulminant liver failure and death.[318–320] Baseline liver function testing (a blood test) and monitoring is usually recommended in people at higher risk of hepatotoxicity adults over 35 years, people who consume harmful levels of alcohol or have pre-existing liver disease.[290] Shorter rifamycin-based regimens demonstrate reduced hepatotoxicity and superior completion rates compared to isoniazid monotherapy.[321] Programmatic data and experience have supported their acceptability and higher completion rates (due to shorter duration and better tolerability) with 3HP or 3HR as the preferred option.[322–325] A 2023 meta-analysis of 277 studies showed that all rifamycin-based regimens were safer than IPT in adults and children with 4R performing the best.[326] Children and adolescents tolerate all TPT very well with low rates of adverse events. The main limitations of rifamycin-based TPTs are their drug-drug interactions if the patient is on other medications, which can be managed with clinician input, including in PLHIV. A meta-analysis of 20 studies of TPT in PLHIV similarly showed that rifamycin-based regimens were as effective and safer with higher rates of completion than IPT in this population.[327]

TPT in pregnancy

TB in pregnancy has been associated with increased maternal, foetal and neonatal morbidity and mortality, including stillbirth, preterm birth and intrauterine growth restriction.[328–330] Whilst treatment outcomes for pregnant people with active TB are generally favourable, there is potentially greater benefit for both mother and foetus in preventing the development of TB through TPT.[63] Large cohort studies demonstrate an approximately two-fold increased risk of TB during pregnancy and early postpartum compared with non-pregnant individuals, with incidence rate ratios of 1.3–1.4 during pregnancy and 1.9–2 postpartum.[61,331]

Current WHO guidelines provide limited recommendations regarding TPT in non-HIV infected pregnant women due to the paucity of evidence, whilst for HIV-positive pregnant women with a positive tuberculin skin test, TPT is recommended.[290] This limited evidence base is a result of the exclusion of pregnant women from most clinical trials. Currently 6-9H, 4R and 3HR are recommended in pregnancy, with trials of 1HP underway.[290]

Observational studies have supported the safety and feasibility of TPT in pregnancy.[63] However, there was a higher rate of adverse pregnancy outcomes (including stillbirth or spontaneous abortion, low birth weight, preterm delivery, or

congenital anomalies) in PLHIV in a RCT allocated to 6H compared with 6H 12 weeks post-delivery.[328] These contrasting findings highlight the urgent need for more robust evidence on safety and efficacy. The administration of TPT during pregnancy therefore requires careful individual risk-benefit assessment. (including stillbirth or spontaneous abortion, low birth weight, preterm delivery, or congenital anomalies)

Newer and emerging TPT regimens

The rifapentine regimens were initially not recommended in children under 2 years, however recent pharmacokinetic studies demonstrated their safety and dosing in all ages.[290,332,333] There has also been recent development of a dispersible 150 mg rifapentine formulation for children.

The ultrashort 1HP regimen shows promise in further increasing uptake and completion, but programmatic experience is still limited. It was shown to be non-inferior to 9H in an RCT conducted in PLHIV, with good tolerability and better completion rates (97% vs 90%).[309] TPT with 1HP is currently only recommended for individuals aged ≥ 13 years based on the initial study, while awaiting results of further studies.[334]

Novel regimens that are the subject of ongoing studies include 4-week oral bedaquiline (BREIF-TB clinical trial) and long acting injectables if bedaquiline, rifapentine and isoniazid that have promising data from mouse models and are moving to human studies.[335–337] Twice-yearly subcutaneous antiretrovirals have been showed to be highly effective and well-tolerated prompting their recent recommendation for the prevention of HIV.[338]

2.3.6 TPT for MDR-TB exposure

The management of contacts exposed to multidrug-resistant or rifampicin-resistant (MDR/RR-TB) tuberculosis presents unique challenges that have evolved significantly with new and recent evidence. Multiple studies have demonstrated that household contacts of MDR-TB have similar rates of TBI to household contacts of DS-TB index cases, highlighting that MDR/RR-TB strains are as transmissible.[339–342]

Historically, WHO guidance was limited by insufficient data, but two landmark RCTs published in 2024 have transformed the evidence base. WHO guidelines now recommend 6 months of daily levofloxacin (6Lfx) as preventive treatment for contacts of MDR/RR-TB cases

Evidence for fluoroquinolone TPT effectiveness and safety

These WHO recommendations are based on strong evidence from the TB-CHAMP and V-QUIN trials, representing a major shift from previous conditional recommendations that relied primarily on observational data and expert opinion. Despite both trials having statistically non-significant results, their results were pooled in a meta-analysis, demonstrating an effect.[125]

The TB-CHAMP trial in South Africa compared 6Lfx versus placebo for preventing tuberculosis in 922 child household contacts (aged <18 years) exposed to MDR-TB. By week 48, 6Lfx showed 56% effectiveness in reducing incident TB, 1.1% vs 2.6% for placebo (HR 0.44, 95% CI 0.15-1.25).[126] Treatment with 6Lfx was well tolerated and safe in children. The V-QUIN trial in Vietnam evaluated 6Lfx in 2,041 adult and child contacts of MDR/RR-TB index cases who had TBI.[127] TPT with 6Lfx demonstrated 45% effectiveness in reducing bacteriologically confirmed TB within 30 months, 0.6% vs 1.1% in placebo (incidence rate ratio 0.55, 95% CI 0.19-1.62). Adverse events were reported in 31.9% of participants on 6Lfx, with the majority (30.2%) grade 1 or 2; and 7.4% stopped 6Lfx due to an adverse event. Notably, both trials demonstrated consistent direction and similar magnitude of protective effect despite neither achieving statistical significance individually, with benefit concentrated within the first 12 months after treatment initiation in both studies. Pooled subgroup analyses revealed generally consistent benefit across age groups, though an important association between levofloxacin use and musculoskeletal adverse events was identified in individuals aged >10 years, with the majority of these events being mild in severity.

Both TB-CHAMP and V-QUIN had lower than expected incidence of TB in contacts, which was likely as result of the impacts of COVID-19 and potentially from the very sensitive screening algorithms used to exclude active TB. Importantly, the investigators collaborated from the outset of both trials to align methodological approaches. This allowed a meta-analysis, which showed 60% effectiveness that was statistically significant (RR 0.40, 95% CI 0.17-0.90), with levofloxacin being generally safe and well-tolerated.[125] It was notable that the benefit of Lfx, compared to placebo, was most marked within 12 months of initiation but waned thereafter. While Lfx was safe and well tolerated in children, in individuals aged >10 years, there was an association between Lfx use and musculoskeletal events, most of which were mild.

These trials complement decades of multiple small observational studies reporting the use of TPT in over 2000 contacts of MDR-TB (see table 1 Seddon et al.).[343] These regimens were primarily fluoroquinolone-based but often included a second drug. A

recent meta-analysis of 11 studies showed a 66% reduction in TB incidence with TPT, consistent with the RCTs.[344]

Pregnancy and Breastfeeding

There is limited data on the safety of prolonged fluoroquinolones in pregnancy but no known evidence of foetal abnormalities. Moxifloxacin (same generation as levofloxacin) is category B3 (Australian Therapeutic Goods Administration) and from the limited to data available, has not been associated with increased risk of congenital teratogenicity.[345] One meta-analysis of observational studies including 2800 pregnant women exposed to fluoroquinolones found no differences in birth defects, spontaneous abortion or prematurity compared to unexposed pregnant women.[346]

Isoniazid for TPT in MDR-TB exposure

The effectiveness of conventional drugs for TPT, particularly isoniazid and rifampicin, in MDR/RR-TB prevention remains unclear, but there may be a potential role.

A recent systematic review and individual-participant meta-analysis (pre-print, not peer reviewed) Martinez et al, of 4,945 contacts exposed to MDR-TB from nine observational cohort studies showed that IPT was 70% effective against incident TB (aHR: 0.30; 95% CI: 0.16–0.56).[347] This effect did not change with adjustment for confounder and decreased over time from 93% in the first year, to 80% in the second year and was non-significant after two years (26% effectiveness).

A prospective cohort study of 2,106 household contacts of DS-TB and MDR-TB index cases who received IPT and followed for one year was conducted in Peru. It showed the reduction in risk of developing TB was 70% (aHR: 0.30; 95%CI: 0.18-0.48) in DS-TB contacts, 81% (aHR: 0.19; 95%CI 0.05-0.66) in MDR-TB contacts and 20% (aHR: 0.80; 95%CI 0.23-2.80) in H-mono-resistant contacts at one year.[348] In a second independent re-analysis by Martinez et al, TB occurred in none of the 76 household contacts who received IPT compared with 3% (8 of 273) of those who did not.

Resistance to anti-tuberculosis drugs is defined by resistance to these agents and measured by mycobacterial growth inhibition to drug via C-DST or presence of associated molecular mutations.[19] However, the mechanism of action of treatment of TBI may be independent of the mechanism of drug killing in active TB.[349] The known mode of action of isoniazid in active TB is to inhibit bacterial cell wall synthesis following activation by enzyme KatG in *M. tuberculosis*.[350] Resistance to isoniazid is conferred by either InhA promoter mutations (usually in mono-H-resistant strains, conferring low level

phenotypic resistance, overcome by high-dose isoniazid) or KatG mutations (found in ~45% of H-resistant strains, conferring high-level resistance).[19] Latent or dormant *M. tuberculosis* lacks a typical cell wall, therefore novel mechanisms of action for isoniazid have been proposed in which the drug has efficacy through host immune system interactions and not only direct mycobacterial killing.[351] These mechanisms and hypotheses remain untested *in vivo* without a better biomarker for TBI.

Future research

Future research is needed to understand potential harms of wider use of long courses of fluoroquinolone therapy. While it has been demonstrated that if screening and exclusion of active TB is implemented well, there is negligible risk of generating resistance in *M. tuberculosis* to the drug used in TPT, ongoing surveillance is important with scale-up.[352,353] The risks mainly lie in developing resistance in other organisms as levofloxacin has a broad spectrum of antibacterial activity. Widespread community use has been shown to be associated with increased fluoroquinolone resistance in common bacterial pathogens.[354,355] Prolonged antibiotic use has shown to alter the gut and respiratory microbiome, with further research needed on the clinical impacts.[356–358]

As it stands, 6Lfx will not be a scalable option for TPT due to the duration of treatment and further trials are underway for different drugs (in the case of fluoroquinolone resistance) and shorter regimens. A clinical trial that compares 6 months of delamanid with 6 months of isoniazid for household contacts of MDR/RR-TB patients is currently enrolling - The Protecting Households on Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (PHOENIx MDR-TB) with results expected in 2027.[359,360] The Bedaquiline Roll-out Evidence in Contacts and People Living With HIV to Prevent (BREACH-TB) trial (NCT0656848) will assess the efficacy and safety of 1 month of daily oral bedaquiline regimen compared with WHO-recommended TPT regimens in close contacts of DS-TB or RR-TB.

Ultimately, what is required is a TPT that is not dependent on determining the resistance profile of the index case. This is of relevance to high transmission MDR/RR-TB settings, where transmission may occur outside the household. The WHO has developed target product profiles for TPT and guidance on evidence generation for new TPT that call for pan-TB regimens. [361,362]

2.3.7 Evidence of impact of TPT on TB epidemiology

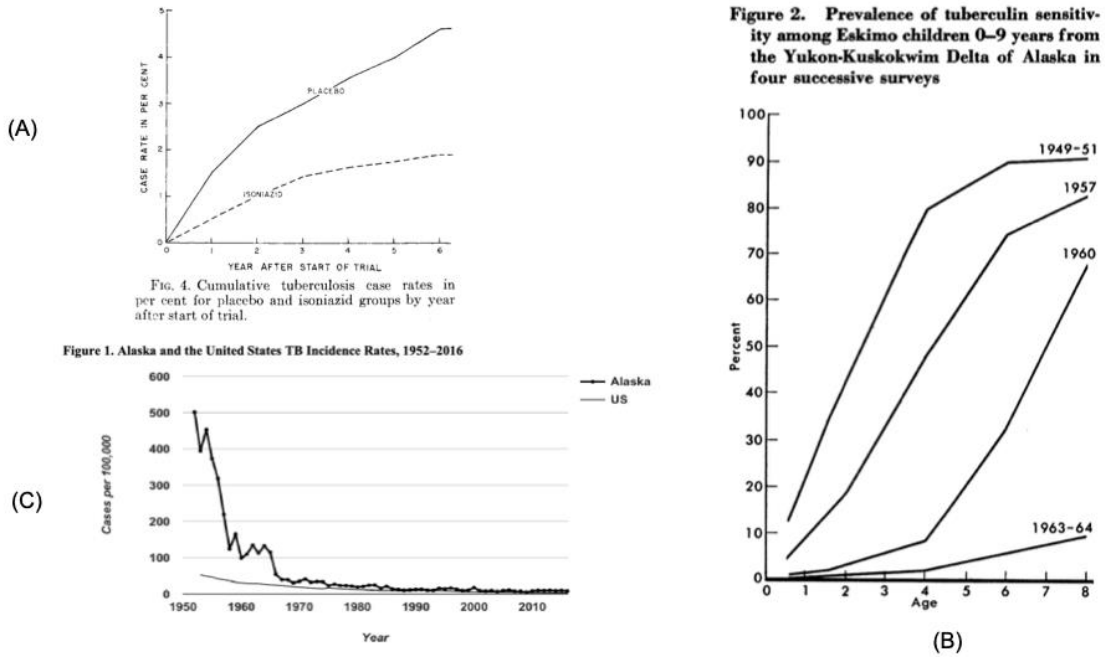
The WHO End TB strategy recommends that TPT is delivered as part of a combination of approaches – screening, TB diagnosis, effectively treating those diagnosed with active TB, and testing and treating high risk groups with TBI, with the aim of reducing TB transmission. TPT expansion in groups at higher risk of progression to active TB, such as contacts and PLHIV, may result in population level impacts on TB transmission. However, the size and contribution of these groups to sustaining the TB epidemic in a high-TB incidence setting is likely to be modest. The provision of TPT must be preceded by systematic screening to exclude active TB and the identification of people eligible for TPT. While WHO recommends systematic screening for active TB in populations with high TB incidence, it does not recommend population-wide testing for TBI infection with TPT.[9,167]

The question of the contribution of TPT to reducing TB transmission and therefore reducing TB incidence or prevalence, as part of a comprehensive strategy of detecting, treating and preventing TB is an important one. As above, the impact of TPT on TB epidemiology can be measured through changes in community TB incidence (case notifications), TB prevalence and/or the prevalence of TBI. Studies that evaluate the population impact of TPT are defined for this review as RCTs with either a population-wide TPT intervention and/or measuring impact at the community-level outside study participants. Studies that are not community-wide interventions and assess TB incidence in individual participants (including groups such as contacts or PLHIV) are not included in this definition.[363–371] Six relevant cluster-RCTs have been identified, with details in Table 2.6.[204,266,270,273,372,373] The TREATS study (TB prevalence survey from POPART trial) was not included, as the TPT intervention was implemented across all arms and implementation fidelity was not specifically evaluated.[212,374]

The strongest evidence for population-level impact comes from historical studies in geographically isolated communities. The seminal study of the population effectiveness of TPT was conducted by the US Public Service (Comstock and Ferebee) in 30 remote and isolated villages in Bethel, Alaska in 1957.[266] This predominantly Indigenous population of approximately 10,000 people had a baseline TB incidence of 1%. Systematic screening with CXR was difficult due to access issues. A community-based cluster-RCT that randomised households to 12H or placebo was conducted in 1957-61, with good adherence (>70% of total doses) among the 7,000 participants. The TB incidence was followed via review of notifications and deaths and demonstrated the benefit of IPT in preventing TB from the first year of the trial (69% effectiveness) which

persisted to year six (67% effectiveness. Following this success, 12H was offered to all households from 1963-64 with 50% of total doses taken in the population.[375] A follow up report in 1979 demonstrated the sustained impact of the intervention in this community and TB notification rates continue to be under 10 per 100,000 through to 2015.[269,376] It is important to note that while the findings support the impact of TPT, the intervention was combined with effective case-finding and treatment (chemotherapy and isolation), making attribution to TPT only difficult. However, four serial TST surveys provide insights into the findings, demonstrating dramatic immediate reductions in community transmission following the cluster-RCT – the prevalence of TBI in children under 3 fell sharply from 34.4% in 1951 to 1.7% in 1960 and <1% in 1964.[268,375] This temporal associate with reduction in transmission does correlate with an effect from TPT. Key figures and charts from these studies in Alaska are shown in Figure 2.4. It must be noted that the communities in Alaska are unique due to their extreme geographical isolation. This is distinct from many high-burden settings where there is considerable population movement, migration and mixing that allows for continued exposures and transmission of TB from new incursions.

Figure 2.4 Key figures from community-wide studies of TPT in Alaska



(A) TB incidence rates in 12H vs placebo (Comstock et al. 1967)[266] (B) TB Infection prevalence by age over four surveys (Hanson et al., 1967)[375] (C) TB Case notification rates 1952-2016 (Chandler et al., 2017)[376]

Table 2.6 Summary of studies evaluating the population-level impact of TPT

Author (year) and country	Study population and setting	Design: Intervention vs Control	Outcomes	Results	Evidence of impact and comments
Nyboe et al. (1963), Tunisia	1958 Urban suburb of Tunis population 25,000 0.7% prevalence bac confirmed TB	1958-1961 cRCT (76 blocks of houses in each arm) to 12H vs placebo. TST, CXR at baseline and 6 monthly follow-up to 24 months n =15,910	Community TB incidence	No statistically significant differences Incidence bac pos TB IPT vs control (0.23% vs 0.31%) 37% reduction in new CXR changes between IPT and control (1.2% vs 1.9%) not statistically significant TBI of participants <15 years not different between 12H and control (10.8 vs 11.7%)	Minimal impact due to poor adherence to intervention 19% of 173 had positive urine detection. Although 80% attended 12 month follow up
Horwitz et al. (1966), Greenland	1956 79 Artic villages, western Greenland (20,990 population) Adolescent and adults ≥15 years TB Incidence nearly 2%	1956: cRCT (village randomisation): Village wide 6H vs placebo Conducted with annual mass screening via ships n = 8,081	Community TB incidence over 6 years	29% reduction in TB incidence (1.2% vs 1.8% placebo) at year 6 83% received 75% of doses	Moderate: population level reduction demonstrated
Comstock et al. (1967, 1979) Hanson et al. (1967) Alaska, USA	1957 30 villages Isolated Indigenous communities TB incidence >1% ~10,000 people	1957-61: cRCT (household randomisation): 12H to all households vs placebo. Quarterly nursing visit. No other new TB interventions. Treatment = H, PAS, hospitalisation. Financial incentives. n = 7,333 (85% coverage of population)	TB incidence (case notifications and deaths) pre-post intervention 3 prevalence surveys of TBI in children 0-3 years	67% reduction in community TB incidence seen from year 1 of intervention Effects persisted 19 years (2.77% initial placebo vs 1.31% initial 12H p<0.001) Reduction in TBI prevalence in	Strong: clear evidence of impact that was sustained. Combined intervention with systematic screening (not described) and treatment. Isolated community and limited generalisability

Author (year) and country	Study population and setting	Design: Intervention vs Control	Outcomes	Results	Evidence of impact and comments
		1963-64: Community-wide approach - all residents offered IPT following CXR screening for active TB N = 6,501 (80% coverage)	Medication adherence index	children: 34% (1951), 14% (1957), 1.7% (1960) 70% of doses taken in RCT and 51% in community-wide program	Author commented limited socio-economic development during initial study period
Cavalcante et al. (2010), Brazil	8 Urban favelas with distinct borders, Rio de Janeiro; Study population 265,000 TB incidence 0.24%	1999-2004 cRCT 4 matched Favellas on TB incidence. Enhanced DOTS-A (contact screening: CXR, TST and TPT with 6H if >17 years) vs standard DOTS Community-randomised trial (22 clusters)	TB case notification rates	15% difference between groups (5% increase DOTS vs 10% decrease DOTS-A; p = 0.04) Only 30% of TB patients participated in the intervention. 4% of 699 DOTS-A contacts had active TB and 178 people completed TPT	Moderate: Statistically significant community-level reduction Surprising to see modest effect size given low numbers; limited follow-up period
Ayles et al. (2013), ZAMSTAR	24 communities (~1.2 million population), Rural and urban	2x2 factorial Enhanced case finding (ECF) and/or household intervention (HIV testing, IPT) vs standard care	Community TB prevalence (population survey)	22% TB prevalence reduction with household intervention (PR 0.78, 95% CI 0.61-0.99)	Moderate: Population prevalence reduction in targeted approach
Churchyard et al. (2014), Thibela TB South Africa	South African gold mines TB incidence ~3% in miners	cRCT: 15 clusters = all workers at a geographically discrete mine, stratified by low or high TB Intervention: TB screening (symptom + CXR → if positive culture), Cluster-RCT (8 clusters) Community-wide IPT vs standard care N=78,744	Cluster level TB incidence 12 month post intervention TB prevalence at study completion	No significant reduction in incidence: intervention 3.02 vs control 2.95 per 100 person years (aRR p=0.71) or prevalence 2.35% vs 2.14% (p=0.90) Direct 58% reduction in TB incidence during TPT (1.10 vs 2.91 per 100 person years) but loss of protection on stopping	None: No sustained community impact High force of infection and re-infection. Powered to detect large difference (40% incidence, 55% prevalence) Other potential factors - mobility (and exposure outside the mine), silicosis, asymptomatic TB

cRCT: cluster randomised controlled trial; bac+: bacteriologically positive; H: isoniazid; PAS: para-aminosalicylic acid; ECF: enhanced case finding; DOTS-A: directly observed treatment short-course with household contact management; PR: prevalence ratio; aRR: adjusted rate ratio

Two similar placebo controlled cluster-RCTs were conducted in different settings in the 1950s. Horwitz et al. randomised 79 Greenland villages to community-wide 6H or placebo and showed a 29% reduction in TB incidence at year six.[270] Nyboe et al. randomised neighbourhood blocks in a Tunisian suburb to 12H or placebo but failed to demonstrate impact due to poor adherence (only 19% had detectable isoniazid in urine), highlighting the critical importance of community uptake and implementation fidelity.[273]

Contemporary cluster-RCTs show more modest and mixed results. Cavalcante et al conducted a cluster-RCT in eight matched urban neighbourhoods (Favellas) of contact investigation with TPT on community TB incidence in Rio de Janeiro, Brazil.[372] Over a 5-year period a statistically significant 15% difference was seen with contact investigation, which was surprising given the small numbers. As described above, the ZAMSTAR study demonstrated a non-significant 22% reduction in community TB prevalence through targeted household intervention that included TPT for PLHIV across 24 communities in Zambia and South Africa.[204]

The Thibela TB study (Churchyard et al.) was designed to break the cycle of TB transmission in South African gold miners who had a TB incidence of 3% by screening for active TB and providing TPT for those without disease.[373] It was a cluster-RCT of workers in 15 geographically discrete gold mines who were randomised to TB screening (symptoms and CXR) and 9H if no active TB, compared with standard of care (passive case finding). Despite 66.2% of 79,000 miners undergoing screening and 87.2% of those starting isoniazid, the intervention showed no significant impact on TB incidence or prevalence 12 months after the intervention. While there was evidence of a direct reduction in TB incidence during TPT, there was a loss of protection on stopping. Post-trial mathematical modelling estimates that all miners were infected with TB at least once, creating an extraordinarily high force of TB infection, with an annual reinfection risk estimated to be 20%.[377] Even with 100% intervention uptake, there would have only been a modest impact. Other contributors may have been high population mobility with miners frequently moving between sites, insufficient statistical power and compounding risks from silicosis and HIV co-infection. It provides crucial insights into the applications and limitations of community-wide TPT.

Impact of TPT in high-risk groups

Studies measuring TPT effectiveness in participants from high-risk subgroups (household contacts, people living with HIV, homeless populations) consistently demonstrate individual protection. While they do not evaluate broader population impact,

they provide additional support to the hypothesis that TPT contributes to transmission reduction in low to moderate TB incidence settings, such as these studies in Brazil. The THRio step-wedged cluster-RCT studies showed a 24% reduction in TB incidence when IPT was added to standard of care in clinics for PLHIV that was sustained for up to 7 years.[365,366] Acuña-Villaorduña et al. conducted a retrospective analysis of 1,097 household contacts and found a 71% reduction in TB among those who received 6H compared to untreated contacts.[363] Teixeira et al. conducted long-term follow-up of 991 Brazilian participants from two RCTs comparing 4R with 9H, showing three-fold higher TB risk among those not completing TPT (2.9 vs 1.1 per 1000 person years observation) over 12 years of follow-up.[369]

Two smaller observational studies of TPT impact from the USA are worthy of note. Cegielski et al. achieved complete elimination of TB in two high-risk Texas neighbourhoods through intensive door-to-door tuberculin skin test screening and TPT among 3,153 residents, reducing TB incidence from 0.40% pre-intervention (1985-1995) to 0.0% post-intervention (1996-2006), while the overall county saw only modest decline from 0.08% to 0.04%.[371] Rendleman's mandated TB screening including TST and TPT program in Portland's homeless community achieved a 89% reduction in case notifications over 10 years, whereas similar populations without this intervention did not show reductions.[367]

Overall, the evidence base for recommending widespread population-level TPT remains weak and there is insufficient high-quality evidence to guide implementation in diverse contemporary settings. Despite strong biological plausibility and clear proof-of-concept from historical studies in isolated populations, there is insufficient high-quality evidence to guide implementation in diverse contemporary settings. The key determinants of success are high coverage, sustained implementation, moderate to high TB incidence (not hyperendemic) and a population with limited mobility (i.e. reduced incursions or mixing). There is a misnomer around ‘durability’ of TPT. The evidence from clinical effectiveness trials, low-incidence settings and the Alaska study has shown that when there is little risk of re-infection, TPT provides durable protection. That is, although it cannot be directly measured, the risk of ‘recrudescent’ TB infection post TPT is low.

What remains to be established is in what epidemiological circumstances, and how, TPT can be combined with interventions – systematic screening for active TB and treatment, and social interventions – to interrupt transmission by preventing the future development of TB in individuals and thereby reducing TB incidence and prevalence.

Policy and implementation considerations

There is an urgent need for resource mobilisation and strengthened health systems to deliver on the commitments for TPT at the second United Nations High-Level Meeting on TB held in 2023. Member States committed to provide 45 million people with TPT between 2023 and 2027, with specific targets for people living with HIV and household contacts of all ages. However, current progress is well short of reaching this.[1]

Successful TPT implementation requires addressing multiple interconnected barriers across health systems, providers, and communities. The WHO recommends a cascade of care approach that supports and monitors individuals as they move through four steps: (1) Identification of people eligible for TPT (2) Screening for and excluding active disease (3) Testing for TB infection (4) Initiation and completion of TPT.[290] A 2016 systematic review of 70 observational cohorts showed major losses at several steps in the TB prevention cascade – 44% completed medical evaluation, 35% recommended for treatment among eligible and 19% completed treatment among those who accepted.[122]

Health and community system barriers to TPT

Resource and capacity constraints limit implementation in high TB-burden settings, including inadequate drug supplies, limited diagnostic capacity for TBI testing, and insufficient healthcare worker training.[378] This is compounded by the lack of prioritisation of preventive interventions, often over curative services in many health systems. Specific to TPT, the individual and population level benefits are not widely known by health care workers and reflects a legacy of a DOTS era policy approach.[379] There is an oft-held concern from TB program managers and clinicians that scaling up TPT risks generating TB drug resistance.[380] This would occur if active TB were inadequately excluded prior to TPT initiation. While there is theoretical concern, programmatic experience and two systematic reviews have shown this not to be the case.[352,353] Community-level barriers include limited access to services (especially if facility-based), socio-economic barriers to care, stigma and challenges in understanding the perceived value of medications when well.[381,382]

Enablers and solutions

A 2020 systematic review identified multiple interventions that improved completion of cascade steps, including patient incentives, home visits, digital solutions and health care worker training.[383] The ACT 4 cluster-RCT demonstrated that a health system intervention of local decision making, standardised evaluation and systems

strengthening increased TPT initiation compared with standard of care in several LMICs.[384]

Decentralised models of care show promise, with community-based delivery achieving higher contact investigation coverage and TPT completion rates than facility-based models, as evidenced by two African cluster-RCTs.[247,385] TPT delivery through existing platforms enhances feasibility and sustainability. Integration with HIV services has been long recommended and successful in a number of settings.[290,386,387] Emerging evidence supports integration with maternal-child health services, diabetes clinics, and nutrition programs.[388,389] This later is critically important given the RATIONS trial demonstration a 39-48% reduction in TB risk with nutritional supplementation in undernourished contacts.[390]

Above all person-centred and community-centred approaches to TPT and TB care are central to the WHO End TB strategy as they improve outcomes and are established on the principles of human-rights. People and household affected by TB have systemic vulnerabilities and biosocial solutions are required, and evidence based. [70,71]

2.4 Conclusion

This review demonstrates that comprehensive epidemic control strategies—integrating systematic screening, effective treatment, and TB preventive treatment—are essential for interrupting TB transmission and achieving elimination in high incidence settings. The evidence shows that prevention which has been long neglected in TB strategies and implementation, must be central to these efforts.

First, our understanding of TB has evolved from a binary model of latent infection and active disease to recognition of a dynamic spectrum that includes early TB states. This paradigm shift underpins modern TB control strategies and research priorities.

Second, systematic screening -whether community-wide or through contact investigation - increases case detection and, when sustained with sufficient coverage, can reduce TB prevalence. The ACT3 trial provides proof-of-concept that intensive screening can achieve substantial transmission reduction even in high-burden settings.

Third, TB preventive treatment has evolved from a neglected and narrowly targeted intervention to a key component of comprehensive TB approach, including in high-incidence settings. However, a diagnostic test for viable *M. tuberculosis* infection that provides risk stratification remains elusive. Regimens for TPT are shorter and better tolerated, with recent stronger evidence of benefit and safety for prevention in MDR-TB

contacts. However, many interventions such as systematic screening for active TB, and testing and treating TBI cannot be easily scaled. While awaiting research and new innovations, optimised implementation of current tools for TB prevention can improve outcomes and if applied as part of comprehensive interventions, have the potential to reduce TB transmission.

Despite the need for a comprehensive strategy to reduce TB transmission, WHO guidelines for implementation focus on each component separately, often with focus on individual risk benefit. This does not provide national or sub-national programs in high-incidence settings with tools to select the optimal combination of interventions based on their epidemiological context. The 2015 Lancet series "How to eliminate tuberculosis" recognised this challenge, proposing integrated epidemic control strategies that combine systematic screening, effective treatment, and wider use of TPT as coordinated packages rather than standalone interventions.[7] These high-intensity interventions that utilise community-wide screening can create a 'tipping point' where TB prevalence drops below transmission-sustaining thresholds. Multiple implementation projects have now demonstrated feasibility, and well-designed rigorous studies are generating evidence.

Implementation must be linked with rigorous research and evaluation to better inform action and demonstrate acceptability, feasibility, and impact. Cost-effectiveness analysis is critical to further resource mobilisation and investment given the high upfront costs and generally low domestic health financing in high TB burden countries. Dowdy and Sohn put forward the view that TB screening has been held to an unreasonable standard of demonstrating population-level impact before investment and that consensus is required on the individual benefits including averted morbidity (post-TB sequelae) and mortality are required for an investment case.[391]

For PNG, particularly South Fly District where TB and MDR-TB have reached crisis levels, this evidence supports the need for a comprehensive detect-treat-prevent response to TB. Building a resilient and sustainable health system will require: (1) containing the TB epidemic and reducing burden through community-centred responses, (2) strengthening the fragile health system through sustained political commitment, financing, and local leadership, and (3) addressing social and structural determinants by putting people and their rights to health, livelihood, and living free from TB at the centre.

Chapter 3: Tuberculosis detection and treatment in South Fly District, Papua New Guinea from 2014 to 2022 – a retrospective cohort study

This chapter is a cohort study that evaluates the programmatic response to TB in South Fly District, PNG, across three distinct phases: the emergency response (2014-16), service strengthening (2017-19) and the COVID-19 pandemic (2020-22). Interventions across this nine-year period focussed on TB detection and treatment, with the addition of active case finding through household contact investigation (Chapter 5) and a single intervention of systematic screening (2017-18). I was instrumental in the development of the programmatic TB strategy, clinical management of MDR-TB, establishment of clinical and programmatic systems and strengthening data collection in a public health role, as part of the emergency TB response, prior to PhD commencement. Two manuscripts have been published related to this chapter, which I led as senior author (conceptualisation, protocol development, analysis plan, wrote initial and final draft of manuscript) and as lead facilitator during operational research training with the first authors-TB program leaders from the WPHA (Appendix 3.3, 3.4). For this PhD chapter, these two datasets have been combined into a single cohort for re-analysis and additional trend, descriptive and logistic regression analyses that I have undertaken, as well as a comprehensive description of programmatic activities that provide more in-depth insights and evaluation of the program.

3.1 Introduction

MDR/RR-TB is a continuing global public health crisis and a major threat to achieving the WHO's target to end the TB epidemic by 2035.[18] MDR/RR-TB is more complex to diagnose and treat than DS-TB, requiring additional resources which place stretched health systems under further strain.[18,147] The emergence and transmission of MDR/RR-TB in PNG is a major challenge with a recognised hot spots in the SFD of Western Province, centred on Daru Island.[143,144]

As detailed in Chapter 1, the alarming reports of MDR/RR-TB in SFD and the decision to transfer patients managed by the Australian clinics in Torres Strait Islands to Daru, led to the PNG NDoH establishing an Emergency Response Taskforce in SFD, under the stewardship of the WPHA supported by implementing partners and technical assistance from the Burnet Institute.

The COVID-19 pandemic caused significant disruption to health care service delivery, particularly in LMICs which often have less resilient health systems.[392,393] The impact on TB services included reduced case detection and poorer treatment outcomes resulting in unprecedented setbacks to global TB control and almost 700,000 excess deaths from TB from 2020 to 2023.[1,394] PNG suffered significant disruption to healthcare and services through workforce impacts, diversion of resources and disrupted systems such as diagnostics and supplies.[392,393]

This chapter aims to comprehensively describe and evaluate the TB response in SFD from 2014 to 2022, where the focus was on strengthening TB detection and treatment and transitioning the TB program model of care from a DOTS approach to one aligned with the WHO End TB Strategy, uniquely, in a high MDR-TB-burden setting. This involved developing a model of community-based care for MDR/RR-TB, introducing innovations in diagnosis, treatment and care for PNG, engaging with the community, understanding the socio-ecological dimensions of TB (Chapter 4), initiating community-based screening through contact investigation (evaluated in Chapter 5) and building capacity in the TB program and for operational research.

TB detection trends and treatment outcomes, including MDR/RR-TB, are evaluated through a retrospective analysis using routinely collected programmatic data. A detailed synthesis of the programmatic interventions for TB is compiled across four periods: pre-emergency response (2011–2014), emergency response (2014–2016), systems strengthening (2017–2019) and COVID-19 (2020–2022). The demographic and clinical characteristics of people with TB and factors associated with unfavourable treatment outcomes, are evaluated. This analysis provides the foundational epidemiological evidence that informed subsequent prevention-focused interventions detailed in Chapters 5-7, demonstrating the evolution from a treatment-centred to a comprehensive detect-treat-prevent approach.

3.2 Methods

Study aim: To describe TB programmatic interventions in South Fly District and evaluate the trend and characteristics of TB case notifications, drug resistance and treatment outcomes from January 2014 to December 2022.

Study objectives:

1. Assess trends in TB case detection disaggregated by demographic and clinical characteristics, 2014-2022

2. Describe the type and timing of programmatic interventions for TB, including during the COVID-19 pandemic, utilising a strategic framework based on program logic, 2011-2022

3. Evaluate the DS-TB and MDR/RR-TB cohort treatment outcomes, 2012-2022

4. Determine factors associated with unfavourable TB treatment outcomes, 2016–2022 (this period was chosen as accurate data on factors, or covariates, were available).

3.2.1 Study Design and study population

A retrospective cohort study of routinely collected programmatic data was conducted for all people registered with DS and MDR/RR-TB in South Fly District, PNG from 1 January 2014 to 31 December 2022. The study participants were all TB treatment registrations at the Daru TB Basic Management Unit (BMU), which provides diagnosis and treatment for people from SFD. For 2014, case-level data on DS-TB patients were not available, and instead aggregate numbers from routine program reports to the NTP were used for case notification rates and treatment outcomes.

3.2.2 Setting

The study was conducted in South Fly District, Western Province, Papua New Guinea. A detailed description of the setting and TB program is provided in Chapter 1.

3.2.3 Strategic framework for programmatic TB interventions

The WPHA TB annual implementation plan (AIP) details activities, areas of partner responsibilities and provides an indicative budget for programmatic TB activities by district. This TB AIP was developed in 2014, at the onset of the emergency response, using a strategic framework for a comprehensive response to reduce TB transmission, including MDR/RR-TB and strengthening the local health system in SFD and strengthening TB services in North and Middle Fly Districts. This strategic framework, or program logic for SFD is displayed in Figure 3.1 and was a conceptual framework adapted from WHO's End TB Strategy, the Zero TB Initiative's approach and the WHO health system building blocks.[7,20,395]. The SFD annual implementation plan goal is to

reduce TB incidence (case notifications) in Daru by 50% by December 2025, with increased capacity in the WPHA and TB program for sustainable systems. There were five strategic interventions:

(1) Model of care to establish a functional patient-centred care delivery system - initial focus was on detection and treatment and care from 2014 to 2016 with the addition of TB prevention from 2017 and building to a comprehensive search, treat, prevent approach in 2020,

(2) Strengthening health system building blocks;

(3) Community engagement;

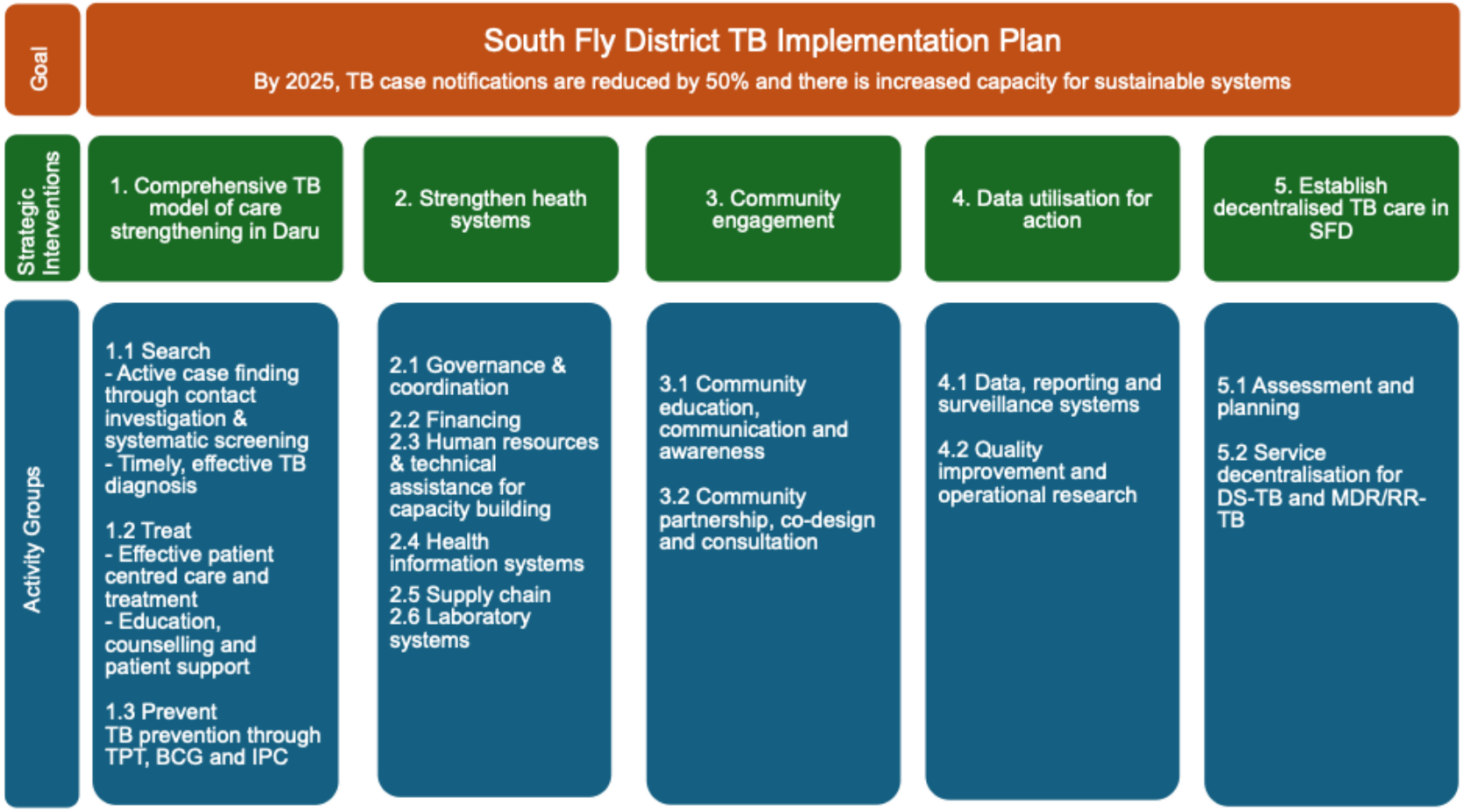
(4) Data utilisation for action; and

(5) Decentralisation of TB services in SFD outside Daru.

Within each strategic intervention, there were activity groups, summarised in Figure 3.1. The SFP TB AIP was reviewed each year by WPHA and partners and updated. It was used for donor-partner alignment and as a framework for monitoring and evaluation of the TB program and partners' contributions.

The TB response and program were led by the WPHA and supported by implementation partners: Burnet Institute for TB technical and implementation support, strategic planning and evaluation, health systems strengthening, community consultation, data utilisation and operational research; and World Vision for community engagement and care.

Figure 3.1 Strategic framework for TB interventions, South Fly District, PNG, 2014–2022



3.2.4 TB diagnosis, treatment and care model

TB diagnosis was centralised at DPH, through a passive case finding model. In 2014, an outpatient clinic known as the 'TB diagnostic centre' was established, allowing referrals from other hospital units (including emergency), community clinics, or for the community to present themselves.

Diagnostic procedures

At the DPH TB diagnostic centre, people with presumptive TB were registered and asked to provide two sputum samples for testing with microscopy using the Ziehl–Nielsen stain. If either specimen weas smear-positive, one sample underwent testing with Xpert MTB/RIF (GeneXpert, Cepheid, Sunnyvale, USA) at DPH. From 2016, all presumptive TB patients were tested with Xpert MTB/RIF. In addition, CXR was performed on all presumptive TB patients. Paediatric patients who are unable to produce sputum and those with signs or symptoms of extra pulmonary TB may undergo further procedures – gastric aspirate, fine needle aspiration of lymph nodes – for testing with a molecular WHO-recommended rapid diagnostic (mWRD). In 2019, Xpert MTB/RIF Ultra replaced Xpert MTB/RIF and in April 2022, Xpert XDR was introduced at Central Public Health Laboratory (CPHL), the national TB reference laboratory in Port Moresby.

All samples with rifampicin resistance detected were transported by air to CPHL for culture (commenced from 2017) and/or to the supranational TB reference laboratory in Brisbane, Australia for culture and drug susceptibility testing (C-DST). At these laboratories, solid and liquid media mycobacterial culture was performed on TB samples using Löwenstein-Jensen slopes with pyruvate and the BACTEC™MGIT™960 (Becton Dickinson Diagnostics, Sparks, MD, USA). Phenotypic DST was performed for rifampicin, isoniazid (0.1 μg/ml low level and 0.4 μg/ml high level), ethambutol and pyrazinamide. For isolates with MDR/RR-TB, second-line DST was performed using amikacin, capreomycin, kanamycin, ofloxacin, ethionamide, para-aminosalicylic acid (PAS) and cycloserine. Detailed laboratory methods, including critical concentrations, have been described elsewhere and follow WHO guidelines.[144,148] The CPHL developed capacity to perform C-DST in 2019; however, this became unavailable from 2020 as the laboratory was not functional. A limited number of C-DST samples were sent to the supranational reference laboratory in Australia from early 2022.[393]

TB Treatment and care procedures

People with TB were managed according to the national TB protocols and WHO guidelines. All people enrolled on TB treatment were counselled and tested for HIV according to national guidelines using rapid diagnostic tests. DS-TB treatment was unchanged over the study period, with a standardised, fixed-dose combination regimen such as 2RHZE/4RH for pulmonary TB.

Treatment of MDR/RR-TB varied over time according to WHO and PNG guidelines. Over the study period, regimens for MDR/RR-TB included four potential standardised regimens:[396] three longer (18-24 months) regimens that could include an injectable agent or newer TB drugs (bedaquiline, delamanid), and a shorter (9-12 months) regimen that included an injectable agent. Patients with pre- or extensively drug-resistant TB (XDR-TB) were treated with longer regimens.

Standardised regimens for MDR/RR-TB were based on phenotypic and genotypic resistance patterns from samples collected at DPH.[144] From 2014-15, the standardised treatment regimen for MDR/RR-TB in Daru was a longer regimen (18 to 24 months) with at least five drugs likely to be effective - kanamycin, levofloxacin, linezolid, clofazimine, cycloserine - and pyrazinamide. Additional available second-line drugs for individualised regimens included capreomycin, moxifloxacin and PAS.

Prothionamide or ethionamide and high-dose isoniazid were not used, based on the unique genotypic and phenotypic resistance patterns in Daru that confer resistance to these drugs.[148] The dominant MDR-TB strain in Daru has been characterised as a modern Beijing lineage with the double accumulation of *inhA* promoter and *inhA* gene mutations. DPH was the first site in PNG to systematically introduce the WHO Group A and B MDR/RR-TB drugs enabling implementation of a bedaquiline-containing longer all-oral regimen with the corresponding phase-out of injectable agents from 2016.[149] The shorter 11-month MDR/RR-TB regimen that was adopted in PNG national guidelines in 2017 was not utilised in Daru, due to the concerns regarding effectiveness given the unique resistance patterns, and the lack of systematic availability of rapid molecular second line TB drug testing to exclude pre/XDR-TB.

Clinical monitoring

All MDR/RR-TB patients underwent baseline clinical and laboratory investigations including blood tests, HIV testing, CXR, audiometry and visual screening as per the national protocol. The protocol required monitoring cultures to be performed monthly in the intensive phase and every 2-3 months in the continuation phase due to resource

(transport, human resources) and laboratory capacity constraints. It was recognised that culture monitoring, especially in the intensive phase was sub-optimal in the program and multiple efforts were made to address this during the study period.

Treatment delivery and care model

From 2016, TB treatment initiation was ambulatory unless patients needed admission for medical or social reasons. Treatment delivery was via regular support from community health workers and treatment supporters at community treatment sites (clinics) in Daru (called Daru Accelerated Response to TB or DART sites). A model of care for MDR/RR-TB treatment and care was developed in response to community and TB patient needs in Daru to provide patient support with directly observed therapy where possible, as per the national protocol. From 2016, person- or patient-centred care has been provided for MDR/RR-TB in Daru, with patient education and counselling, daily meals, adverse event management and referral.[150] For patients residing outside Daru, treatment was initiated at Daru BMU, but self-administered MDR/RR-TB treatment (SAT) could be provided for periods for selected patients who could be monitored by a family or community treatment supporter and return monthly for clinical review .

Community engagement and involvement

A peer counselling model was introduced in 2016 involving people who have been affected by, living with or having survived TB, known as PALS, who are trained and mentored to provide education and counselling support.[150] Locally tailored education materials including visual tools were developed and tested with the community, with guides created for standard counselling sessions. Due to limited health literacy and linguistic diversity (with more than three languages: Tok Pisin, Kiwai and English, plus local dialects) in the transboundary region of the South Fly District, visual tools and aids have been particularly important, including the use of the term ‘sleeping TB’ to explain TBI concepts. Community education campaigns have included promotion from the town mayor and local leaders, public education sessions at churches, schools, sports events, and local radio. A patient representatives’ group was formed in 2015, as a mechanism to provide feedback on the TB services to the program. A community TB stakeholder alliance for Daru was formed in 2016 consisting of representatives from local businesses, churches and not-for-profit organisations to raise awareness of TB, provide input and support the TB program activities and plans.

Active case finding

Active case finding or community-based systematic screening activities occurred throughout the study period. Household contact investigation of bacteriologically confirmed pulmonary TB index cases was introduced in 2016 and was previously evaluated up to 2018.[397] This involved symptom screening of household contacts of DS and MDR/RR-TB and referral to DPH for diagnosis with treatment initiated if TB was detected. Tuberculosis preventive treatment (TPT) was provided for young (<5 years) child contacts of index cases with DS-TB from 2016 and MDR/RR-TB from 2019 to 2020, with an evaluation conducted as part of this thesis (Chapter 5).

A community-based systematic screening initiative (SSI) was conducted over 12 months from 2018 to 2019 with the findings recently published.[151] The SSI screened Daru residents aged 10 years and above in the community for active TB using a single fixed-point chest radiography (CXR) with a computer-aided detection system (CAD4TB v6, Delft Imaging Systems, Netherlands). People with an abnormal CXR defined as a CAD4TB score ≥ 40 or people who screened positive for TB-related symptoms were referred to the hospital for TB diagnosis and treatment.

3.2.5 COVID-19 in PNG

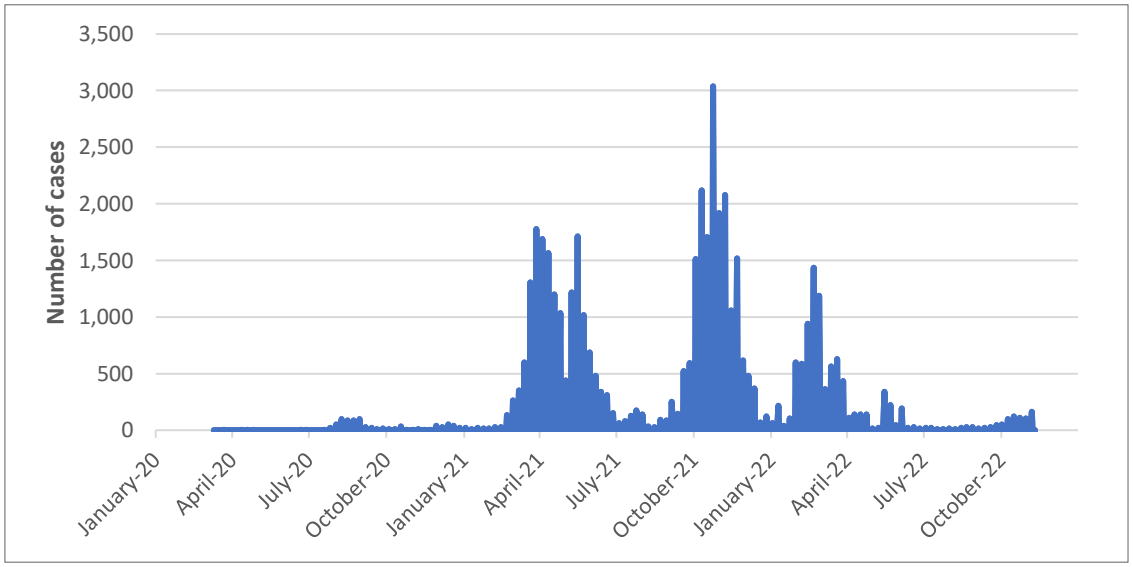
PNG experienced a small wave of COVID-19 in 2020 and three major waves of reported COVID-19 cases and deaths; February to May 2021, August to November 2021, and January to May 2022, consistent with the emergence of successive variants of concern, displayed in Figure 3.2.[392] As of April 2023, when routine reporting stopped, there were over 47,000 confirmed cases and 670 deaths reported from COVID-19.[398] However, this is likely a large but undetermined underestimate of the true burden of COVID-19 in PNG due to limited testing capacity, limited contact tracing and underreporting.[398] Access to molecular testing was very limited across PNG despite the distribution of Xpert Xpress SARS-CoV-2 tests to provinces in May 2021. At the same time, rapid antigen tests (RATs) were distributed and required for health care workers to perform swabbing. Testing rates remained very low with barriers such as misinformation, lack of community trust, access, and logistic and supply issues.[399]

Health system strain was reported with hospitals overwhelmed across the second and third waves. The national government declared a state of emergency in response to COVID-19 on 23 March, 2020, with international border closures, quarantine, a National Pandemic Act and international resource mobilisation. On three occasions in the first 100

days, nationwide lockdowns for up to two weeks were instituted where health services only opened to critical and emergency services.[392] After this time, only localised lockdowns were implemented, but were less significant in scale or duration. In August 2020, the 'Niupela Pasin' prevention and mitigation strategy was introduced, which emphasised face masks, social distancing and hand hygiene. Isolation and quarantine were generally not enforced, and community uptake of public health measures was generally very low, noting variation across the provinces. COVID-19 vaccination in PNG commenced in March 2021, but COVID-19 vaccination rates remained alarmingly low, with 7.1% of the population receiving a single dose.[392] In February 2022, government policy shifted to a reduction in public health measures and testing and international borders were re-opened.

In Western Province, a high proportion of national cases were reported across the pandemic, largely due to the availability of testing in the private mining sector in North Fly District, where the first provincial cases were reported in April 2020.[400] Due to limited testing availability, reliable testing and reporting of cases was not available.

Figure 3.2 COVID-19 notifications in Papua New Guinea, 2020-2022



Source: World Health Organisation (2024); Population based on various sources (2024) – with major processing by Our World in Data

3.2.6 Study Definitions

The study definitions used for TB registration and outcomes were as per the 2022 consolidated World Health Organisation definitions[396] and the 2017 PNG TB guidelines,[148,401] noting the evolution of MDR/RR-TB reporting definitions over time.[402,403]

Appendix 3.1 contains detailed data definitions. There was one key adaptation where an operational definition was used to modify the definition of failure for MDR/RR-TB in SFD. Patients who had a permanent regimen change of at least two anti-tuberculosis drugs were not classified as treatment failures if the patient was responding to treatment with no evidence of clinical or microbiological failure. Clinical audits (unpublished) showed that this drug change occurred for two reasons: (1) from 2016 onwards, most of the cohort was being changed from the injectable agent to bedaquiline (which became part of the PNG protocol in 2016) and/or (2) changes occurred to a drug not considered to be core in the regimen (e.g., PAS or pyrazinamide).

Primary residential address was recorded during registration and coded to the 2021 census units. The hierarchical structure used in the PNG census is province, district, local level government (LLG), ward and census unit (village).[133] Treatment outcomes were categorised as favourable (cure or treatment completed with the sum being "treatment success") or unfavourable (failed, died-for any reason before starting or during the course of treatment, lost to follow-up or not evaluated).

Programmatic activities and interventions are described using the strategic framework for TB interventions in SFD (Figure 3.1) and according to a baseline and three periods:

1. Baseline from 1 January 2011 to 31 December 2013;
2. Period 1, 'Emergency Response' from 1 January 2014 to 31 December 2016;
3. Period 2, 'Service Strengthening' from 1 January 2017 to 31 December 2019; and
4. Period 3, 'COVID' from 1 January 2020 to 31 December 2022.

Period 2 is referred to as "pre-COVID" when compared with the COVID period.

3.2.7 Data collection, variables and analysis

At Daru BMU, TB cases were recorded in paper-based programmatic registers and an electronic medical record system (EMRS; Bahmni v.0.87; Thoughtworks, Chicago, IL, USA). Data were exported from the TB treatment registration dataset and cleaned and analysed using STATA version 18 (Stata Corp, College Station, TX, USA). Numbers and proportions were calculated for notified cases and outcomes, by annual cohort. Statistical significance between two proportions was tested using standard error.

All treatment episodes for TB were included unless they were subsequently given an outcome of 'no active TB' (for both DS-TB and MDR/RR-TB patients). The data variables collected included age, sex, place of residence at time of registration, date of TB treatment initiation (enrolment), anatomical TB site (pulmonary, extrapulmonary), TB treatment history (new or previous TB treatment), diagnosis method (bacteriologically confirmed or clinically diagnosed), HIV status at enrolment, resistance profile and TB treatment outcomes. Numbers and proportions were calculated for cases registered, characteristics and treatment outcomes. Chi-square tests were used to assess differences in proportions across periods for categorical variables, with statistical significance set at $p<0.05$.

Annualised TB case notification rates (CNR) were calculated based on annual population data from the 2021 national census according to the address provided at registration.[133] The population denominators were 19,397 people for Daru and 84,435 people for SFD. The trend in TB CNR over time was assessed using linear regression for the overall trend. The mean annual CNR was calculated for each period. Differences between periods were assessed using one-way analysis of variance. Statistical significance was set at $p<0.05$.

Program activities and interventions implemented over the study period were extracted and synthesised from annual provincial TB and implementation partner project reports and described using the strategic framework over the baseline and three time periods outlined above. COVID-19 interventions were described in narrative format.

Univariable and multivariable logistic regression analyses were conducted to assess risk factors for unfavourable TB treatment outcomes. The outcome variable was dichotomised as favourable (cured or treatment completed) versus unfavourable (died, lost to follow-up, treatment failed, or not evaluated). Eight independent covariates were

included in the model: age group (0-4, 5-14, 15-34, 35-54 [reference], >54 years), sex (female [reference], male), residence (Daru [reference], outside Daru), TB resistance (DS-TB [reference], MDR/RR-TB), previous TB treatment (no [reference], yes), diagnosis method (bacteriologically confirmed [reference], clinically diagnosed), TB site (pulmonary [reference], extrapulmonary), and HIV status (negative [reference], positive). Data completeness was assessed for all key variables. Unknown or missing values for covariates were included in descriptive analyses but excluded from the regression models. All covariates were included in the multivariable model regardless of their significance in univariable analyses, given their clinical and programmatic relevance, therefore backward or forward stepwise regression was not performed. Results are presented as adjusted odds ratios (aOR) with 95% confidence intervals (95%CI) and p-values. A p-value of < 0.05 was considered statistically significant.

3.2.8 Ethics

Separate ethical approval for the relevant components of this combined retrospective analysis was obtained from the PNG Medical Research Advisory Council.[151,404,405]

3.3 Results

3.3.1 TB epidemiology

There were 4,847 people registered for TB in the study period. Figure 3.3 shows TB case notifications by year disaggregated by age and Figure 3.4 by drug-resistance. The largest number of notifications were in the 15 to 34 years age group across the study period. The notifications of MDR/RR-TB were stable over the study period, following an increase in detection in 2015 from 2014. Table 3.1 displays the clinical and demographic characteristics of people registered with TB from 2014 to 2022 in SFD, and Table 3.2 displays characteristics per period.

The CNR for all TB from 2014 to 2022 was 638 per 100,000 for SFD, 1,815 per 100,000 for Daru and 122 per 100,000 people for MDR/RR-TB in SFD. The overall trend showed an average annual decline of 15.4 cases per 100,000 population (95% CI: -32.1 to 1.3), however due to substantial year to year variation, this was not statistically significant (p=0.068). The mean CNR per 100,000 for SFD in each period was: 665 in the emergency response, 654 in the service strengthening and 592 per 100,000 in COVID and the differences between periods were not statistically significant (p=0.192). The CNR of bacteriologically confirmed TB (2015 to 2022) in SFD was 350 per 100,000.

MDR/RR-TB comprised 19.2% of all TB, increasing from 11.8% in 2014 to 24.8% in 2016 before stabilising around 20%. The proportion of MDR/RR-TB among bacteriologically confirmed cases (2015 to 2022) was 32.1%. The proportion of new cases among MDR/RR-TB was 60.9% (range: 37.4% to 78.4%). The proportion of MDR/RR-TB among new cases was 14.9%, (95%CI 13.7–16.2) and among previously treated cases was 61.5% (95% CI 56.6–66.2). The proportion of fluoroquinolone-resistant TB (pre-XDR and XDR-TB) was 1.4% of total notifications, 2.4% of bacteriologically confirmed TB (2015 to 2022) and 7.0% of all MDR/RR-TB. There was one person identified with mono-resistant TB (to isoniazid) who was treated with a DS-TB regimen, and, therefore was classified as DS-TB.

Almost one half (47.2%) of the case notifications were in older adolescents or young adults aged 15-34 years and 20.7% of case notifications were in children (<15 years). Around two-thirds (67.2%) of all people treated for TB were resident on Daru. While pulmonary TB was predominant, extrapulmonary TB was common (37.5%). Extra-pulmonary TB was significantly associated with younger age ($p<0.001$) - the proportion of extrapulmonary TB was highest among children <10 years (45.4%), followed by adolescents aged 10-19 years (38.6%), and lowest among adults ≥20 years (31.9%).

There was a 27.5% reduction in case notifications over the emergency response period (Period 1 from 2014 to 2016) followed by a 24.8% increase during the service strengthening period (Period 2 from 2016 to 2019), which represented the highest notifications across the three periods. COVID impacts are described below. Bacteriologically confirmed cases increased from 41.5% in 2015 to 76.1% in 2022. HIV testing coverage improved over time and HIV positivity remained relatively low (2.1% overall) among those tested.

The proportion of cases in children aged 0-14 years increased from 20.0% in the emergency response period to 23.3% in 2017-2019, before declining to 18.3% during the COVID period ($p=0.002$). The changes in proportions were particularly pronounced in young children aged 0-4 years (7.0%, 10.0%, and 5.3% respectively, $p<0.001$), while remaining stable in children aged 5-14 years ($p=0.962$).

The proportion of drug-resistant TB remained relatively stable across these periods (18.3%, 18.4%, and 17.0% respectively, $p=0.521$). The proportion of cases from Daru fluctuated across periods, from 70.6% in 2015-2016 to 63.5% in 2017-2019, before increasing to 69.0% in the COVID period ($p<0.001$). Bacteriologically confirmed cases showed consistent improvement, increasing from 53.1% to 72.1% ($p<0.001$) between

the emergency response and COVID periods. The proportion of cases registered as new increased over time from 77.6% to 89.3% (p<0.001). The proportion of pulmonary TB showed slight variation across periods (62.1%, 64.9%, and 60.3%, p=0.021). Among those tested, HIV positivity remained relatively low but increased slightly from 1.3% in the early period to 2.1% in the COVID period (p=0.031).

3.3.2 TB and MDR/RR-TB treatment outcomes

Table 3.3 and Figure 3.5 display the treatment outcomes for DS-TB enrolled on treatment from 1 January 2014 to 31 December 2018. Table 3.4 and Figure 3.5 display the MDR//RR-TB treatment outcomes. Treatment success rate (favourable outcomes) was 53% for DS-TB and 68.4% for MDR/RR-TB in 2014, increasing to 85.7% and 88.3% in 2016 and was maintained at this level until the end of the study period.

Overall, the proportion of people with an unfavourable TB treatment outcome was 20.3%, comprising lost to follow-up (LTFU, 6.8%), not evaluated (5.8%), died (5.6%) and failure (2.1%). There were a total of 242 people with TB who died during the study period. Among people with MDR/RR-TB, 9.0% died and 5.4% were LTFU. Among people with DS-TB, 4.5% died and 6.9% were LTFU.

Table 3.5 shows the factors associated with unfavourable outcomes with univariable and multivariable regression analysis. The factors associated with unfavourable outcomes in the multivariable analysis were clinically diagnosed TB (2.4 times compared to bacteriologically confirmed), HIV-positive status (2.4 times compared to HIV negative), residence outside Daru (1.8 times compared to Daru residents), male gender (1.6 times) and having MDR/RR-TB (1.4 times). TB in children (0-14 years) was associated with more favourable outcomes compared with adults (35-54 years) and in adults, unfavourable treatment outcomes were more common in older age groups.

3.3.3 TB programmatic interventions and COVID-19 impact

Table 3.6 summarises the programmatic interventions that have been implemented since the emergency response in 2014 by baseline and three periods: baseline (2011-2013), emergency response (2014-16), strengthened systems or pre-COVID (2017-19) and COVID (2020-23), grouped according to the strategic framework used for response planning and monitoring. Detailed programmatic descriptions of these four periods are provided in supplementary table in Appendix 3.2.

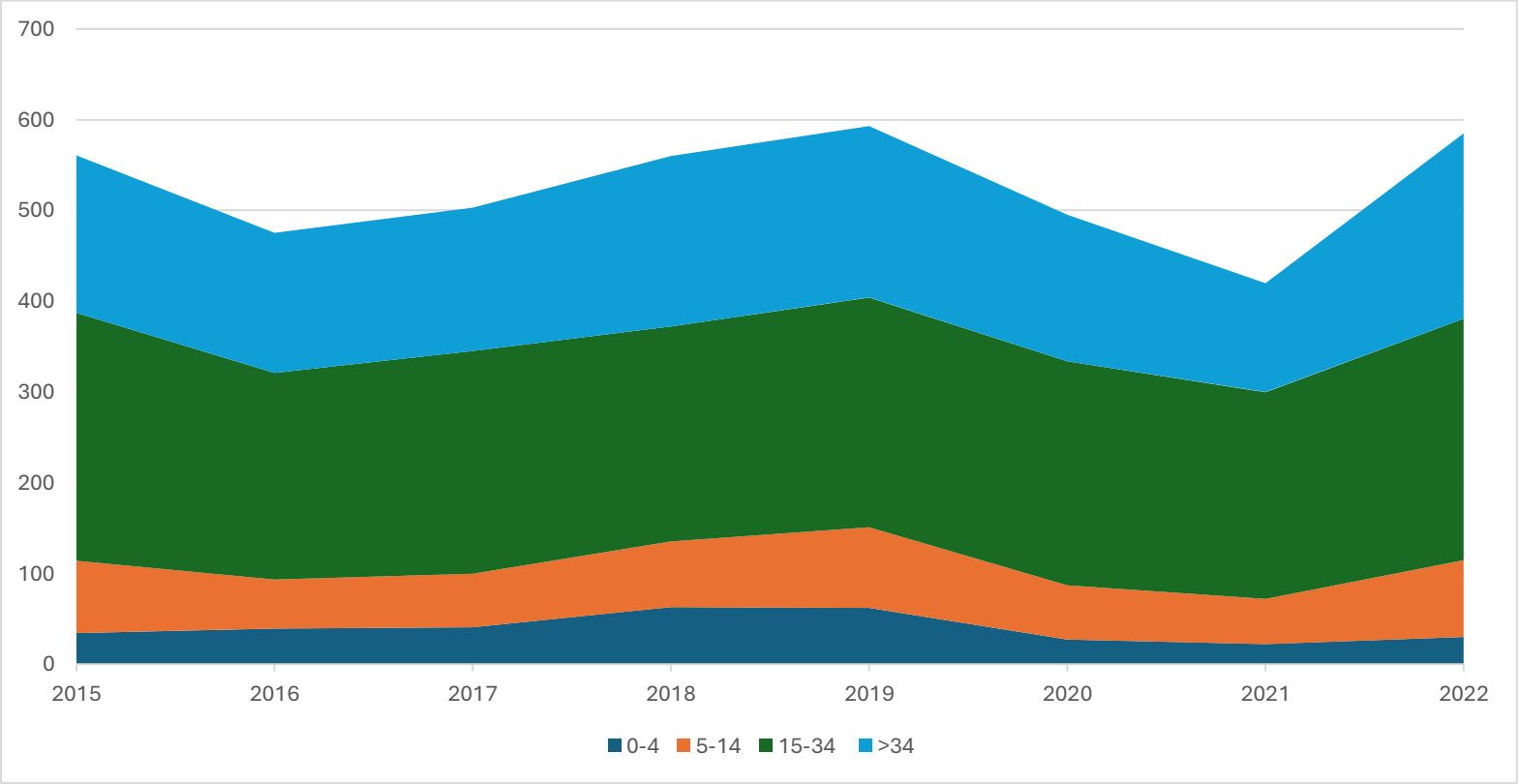
There was a 29.2% reduction in case notifications from 2019 to 2021 with recovery in 2022. This disruption was greater in DR-TB (37.0%) compared with DS-TB (27.0%). Case notification rate decreased by 9.5% from pre-COVID to COVID.

Compared to the pre-COVID period, in the COVID period there were statistically significant but small increases in residence in Daru and bacteriological confirmation and decreases in TB notifications in young children (0-4 years), pulmonary TB and DR-TB. The decrease in MDR/RR-TB in COVID was offset by an increase in RR-TB. Pre-XDR and XDR-TB did not change significantly.

Overall treatment success rate was 86.5% for DS-TB and 83.6% for DR-TB. The treatment success rates for each period for all TB were 69.4%, 85.9% and 87.4%, respectively and is represented in Figure 3.7. Treatment success rates, TB deaths and loss to follow-up did not change significantly during the COVID period.

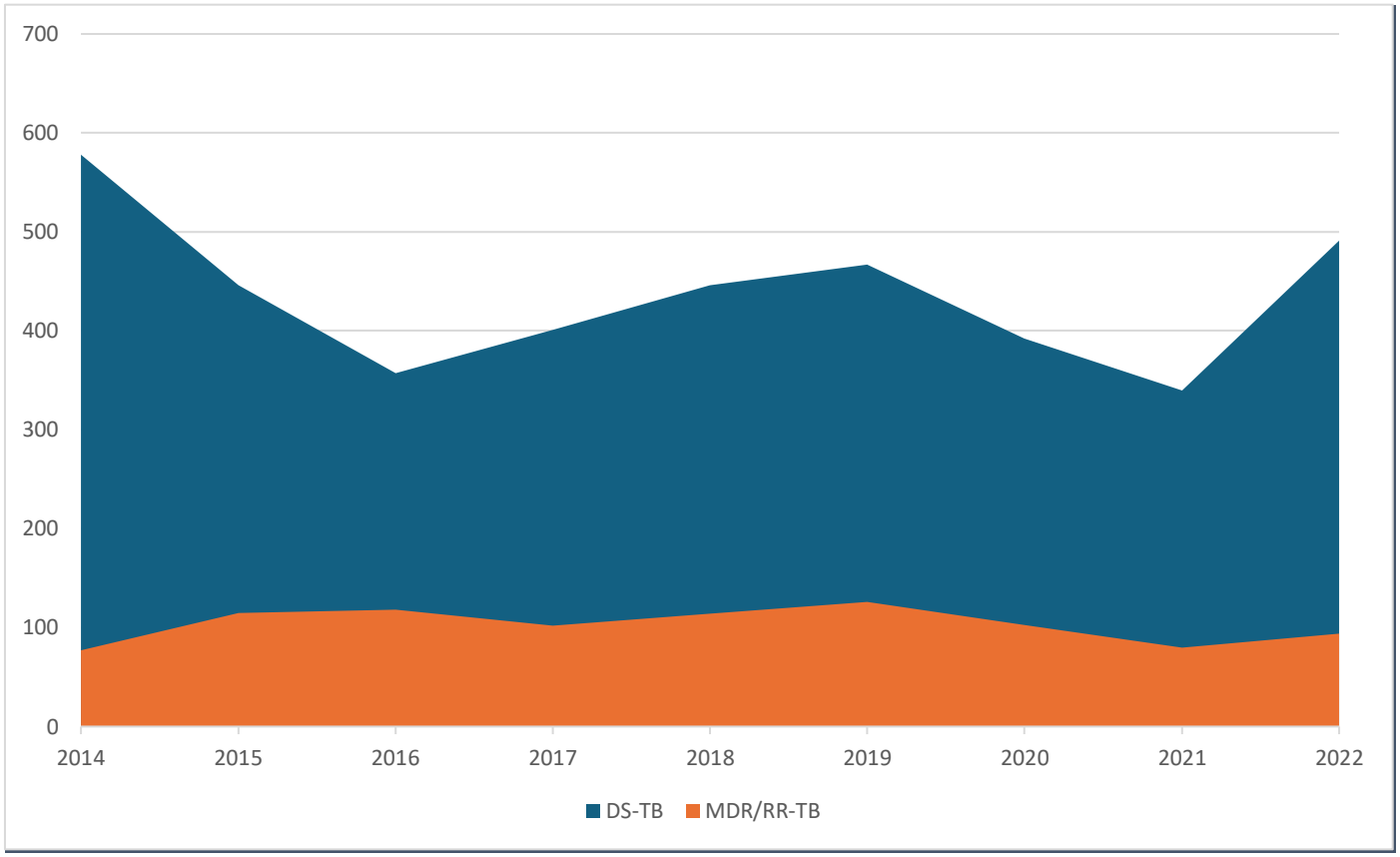
There were impacts on TB services through 2020-21, with a return to pre-COVID activities in 2022. During the COVID-19 period in SFD, the duration of lockdowns was limited to the initial national period in 2020. Population movement may have been reduced with the reduction in domestic travel and border closures to the Torres Strait (from March 2020 to late 2022). There was a notable and significant impact on the health workforce which included increased absenteeism (isolation and quarantine during waves), diversion of staff to the COVID-19 response, and the reduction in services. During the COVID period, there was an observed increase in community mask use and significant community engagement and health promotion on prevention measures. There was a concerted vaccination rollout in SFD and the PNG-Australia treaty villages with moderate uptake, compared with other provinces.

Figure 3.3 TB notifications by age group, 2015-2022, South Fly District, Papua New Guinea



*includes 7 missing coded as >34

Figure 3.4 TB notifications by resistance profile, 2014-2022, South Fly District, Papua New Guinea



DS-TB: Drug-susceptible TB; MDR/RR-TB: multidrug and rifampicin-resistant TB

Table 3.1 Clinical and demographic characteristics of people with TB in South Fly District, 2014-2022

Characteristic		2014	2015	2016	2017	2018	2019	2020	2021	2022	Total[1]
Total		655	561	475	503	560	593	495	420	585	4,847
Median age (years)		-	30	24	26	25	25	25	24	26	25
CNR (per 100,000 population)											
	SFD (All TB)	766	665	563	596	663	702	586	497	693	621
	SFD (DR-TB)	91	136	140	121	135	150	122	95	111	135
	Daru (All TB)	-	2,047	1,722	1,474	1,882	2,062	1,614	1,552	2,170	1,806
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age Group											
	0-4 years	-	34 (6.1)	39 (8.2)	41 (8.2)	63 (11.2)	62 (10.5)	27 (5.5)	22 (5.2)	30 (5.1)	318 (7.6)
	5-14 years	-	80 (14.3)	54 (11.4)	59 (11.7)	72 (12.9)	89 (15.0)	60 (12.1)	50 (11.9)	85 (14.5)	549 (13.1)
	15-34 years	-	273 (48.7)	228 (48.0)	245 (48.7)	237 (42.3)	253 (42.7)	247 (49.9)	228 (54.3)	266 (45.5)	1,977 (47.2)
	35-54 years	-	142 (25.3)	120 (25.3)	121 (24.1)	135 (24.1)	134 (22.6)	132 (26.7)	95 (22.6)	169 (28.9)	1,048 (25.0)
	≥55 years	-	27 (4.8)	34 (7.2)	37 (7.4)	53 (9.5)	53 (8.9)	29 (5.9)	25 (6.0)	35 (6.0)	293 (6.0)
	Unknown	-	5 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.2)
Sex											
	Female	-	283 (50.4)	224 (47.2)	236 (46.9)	294 (52.5)	265 (44.7)	229 (46.3)	188 (44.8)	277 (47.4)	1,997 (47.6)
Residence	Daru	-	397 (70.8)	334 (70.3)	286 (56.9)	365 (65.2)	400 (67.5)	313 (63.2)	301 (71.7)	421 (72.0)	2,817 (73.8)
	Outside Daru	-	162 (28.9)	140 (29.5)	217 (43.1)	193 (34.5)	193 (32.5)	182 (36.8)	119 (28.3)	164 (28.0)	999 (26.2)
	Unknown	-	2 (0.4)	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)

Characteristic		2014	2015	2016	2017	2018	2019	2020	2021	2022	Total[1]
	South Fly District	-	-	-	479 (95.2)	541 (96.6)	577 (97.3)	468 (94.5)	409 (97.4)	571 (97.6)	-
	Other or Unknown	-	-	-	24 (4.8)	19 (3.4)	16 (2.7)	27 (5.5)	11 (2.6)	14 (2.4)	-
HIV Status	Negative	-	333 (59.9)	310 (66.1)	414 (82.3)	518 (92.5)	552 (93.1)	446 (90.1)	395 (94.0)	549 (93.8)	3,516 (83.9)
	Positive	-	8 (1.4)	5 (1.1)	13 (2.6)	14 (2.5)	18 (3.0)	13 (2.6)	8 (1.9)	10 (1.7)	89 (2.1)
	Unknown	-	215 (38.7)	154 (32.8)	76 (15.1)	28 (5.0)	23 (3.9)	36 (7.3)	17 (4.0)	26 (4.4)	576 (13.7)
Treatment	New	-	412 (73.4)	392 (82.5)	454 (90.3)	500 (89.3)	515 (86.8)	442 (89.3)	368 (87.6)	529 (90.4)	3,610 (86.1)
history	Previously treated	-	143 (25.5)	83 (17.5)	48 (9.5)	58 (10.4)	70 (11.8)	47 (9.5)	51 (12.1)	54 (9.2)	556 (13.3)
	Unknown	-	6 (1.1)	0 (0.0)	1 (0.2)	2 (0.4)	8 (1.3)	6 (1.2)	1 (0.2)	2 (0.3)	26 (0.6)
Disease Site	Pulmonary	-	341 (60.8)	302 (63.6)	371 (73.8)	346 (61.8)	358 (60.4)	260 (52.5)	272 (64.8)	372 (63.6)	2621 (62.5)
	Extrapulmonary TB	-	220 (39.2)	173 (36.4)	132 (26.2)	214 (38.2)	235 (39.6)	235 (47.5)	148 (35.2)	212 (36.2)	1,570 (37.5)
	Unknown	-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.0)
Diagnosis method	Bacteriologically Confirmed	-	233 (41.5)	317 (66.7)	345 (68.6)	332 (59.3)	349 (58.9)	325 (65.7)	311 (74.0)	445 (76.1)	2,657 (63.4)
	Clinically Diagnosed	-	329 (58.5)	158 (33.3)	158 (31.4)	228 (40.7)	244 (41.1)	166 (33.5)	106 (25.2)	139 (23.8)	1,528 (36.5)
	Unknown	-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	3 (0.7)	1 (0.2)	8 (0.2)
Resistance	DS-TB[2]	578 (88.2)	446 (79.5)	357 (75.2)	401 (79.7)	446 (79.6)	467 (78.6)	392 (79.2)	340 (81.0)	491 (83.9)	3,918 (80.4)
	MDR/RR-TB	77 (11.8)	115 (20.5)	118 (24.8)	102 (20.3)	114 (20.4)	126 (21.4)	103 (20.8)	80 (19.0)	94 (16.1)	929 (19.2)
	MDR-TB	47 (7.2)	87 (15.5)	88 (18.5)	60 (11.9)	85 (15.2)	64 (10)	22 (4.4)	35 (8.3)	24 (4.1)	512 (10.6)

Characteristic	2014	2015	2016	2017	2018	2019	2020	2021	2022	Total[1]
RR-TB	28 (4.3)	19 (3.4)	20 (4.2)	30 (6.0)	21 (0.8)	45 (7.6)	75 (15.2)	39 (9.3)	61 (10.3)	338 (10.6)
Pre-XDR-TB	0 (0.0)	1 (0.2)	4 (0.8)	8 (1.6)	1 (0.2)	6 (1.0)	1 (0.2)	5 (1.2)	7 (1.2)	33 (0.7)
XDR-TB	2 (0.3)	8 (1.4)	6 (1.3)	4 (0.8)	6 (1.1)	4 (0.7)	1 (0.2)	1 (0.2)	0 (0.0)	32 (0.7)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	7 (1.2)	4 (0.8)	0 (0.0)	2 (0.3)	14 (0.3)

CNR: case notification rate; SFD: South Fly District; DR-TB: drug-resistant tuberculosis; DS-TB: drug-susceptible tuberculosis; MDR-TB: multidrug-resistant tuberculosis; RR-TB: rifampicin-resistant tuberculosis; Pre-XDR-TB: pre-extensively drug-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis

[1]Totals and percentages for age group, sex, residence, HIV status, treatment history, disease site and diagnosis method are for 2015 to 2022

[2]DS-TB includes 1 person with mono-resistant TB (isoniazid)

Table 3.2 Clinical and demographic characteristics of people with TB in South Fly District, by period, 2014-2022

	Emergency response (2014-2016)	**Service Strengthening (pre-COVID) (2017-2019)**	**COVID (2020-2022)**	**p-value[1]**
Notifications				
Total	1,691	1,656	1,500	-
Annual mean (range)	564 (475-655)	552 (503-593)	500 (420-585)	-
CNR per 100,000 (range)	665 (563-766)	654 (596-702)	592 (497-693)	0.192
Demographics[2]	**n (%)**	**n (%)**	**n (%)**	
Daru residence	731 (70.6)	1,051 (63.5)	1,035 (69.0)	<0.001
Age 0 - 4 years	73 (4.3)	166 (10.0)	79 (5.3)	<0.001
Age 5 -14 years	134 (7.9)	220 (13.3)	195 (13.0)	0.962
Age 0 - 14 years	207 (12.2)	386 (23.3)	274 (18.3)	0.002
Case Characteristics				
New (no previous treatment)[2]	804 (77.6)	1,469 (88.7)	1,339 (89.3)	<0.001
Bacteriologically confirmed[2]	550 (53.1)	1,026 (62.0)	1,081 (72.1)	<0.001
Pulmonary TB[2]	643 (62.1)	1,075 (64.9)	904 (60.3)	0.021
Drug-resistant TB	310 (18.3)	305 (18.4)	255 (17.0)	0.521
HIV Positive[2]	13 (1.3)	45 (2.7)	31 (2.1)	0.031
HIV Negative[2]	643 (62.1)	1,484 (89.6)	1,390 (92.7)	<0.001
HIV Status Unknown[2]	369 (35.6)	127 (7.7)	79 (5.3)	<0.001

CNR: case notification rate; SFD: South Fly District; DR-TB: drug-resistant tuberculosis

[1] chi-square tests for proportions, ANOVA for continuous variables

[2]Data incomplete for 2014, percentages based on data from 2015-16

Table 3.3 Treatment outcomes for people with DS-TB, South Fly District, 2014–2022

	2014 n (%)	2015 n (%)	2016 n (%)	2017 n (%)	2018 n (%)	2019 n (%)	2020 n (%)	2021 n (%)	2022 n (%)	Total n (%)
Favourable	312 (54.1)	309 (68.8)	306 (85.7)	351 (87.5)	388 (86.8)	398 (85.4)	344 (87.5)	303 (88.6)	422 (85.9)	3,133 (79.8)
Completed	NA	240 (53.5)	253 (70.9)	297 (74.1)	344 (77.0)	347 (74.5)	267 (67.9)	214 (62.6)	313 (63.7)	2,275 (58.0)
Cure	NA	69 (15.4)	53 (14.8)	54 (13.5)	44 (9.8)	51 (10.9)	77 (19.6)	29 (26.0)	109 (22.2)	546 (13.9)
Unfavourable	266 (46.0)	140 (31.2)	51 (14.3)	50 (12.5)	59 (13.2)	68 (14.6)	49 (12.5)	39 (11.4)	69 (14.1)	791 (20.2)
Died	21 (3.6)	29 (6.5)	20 (5.6)	21 (5.2)	13 (2.9)	24 (5.2)	24 (6.1)	11 (3.2)	13 (2.6)	176 (4.5)
Failed	10 (1.7)	12 (2.7)	8 (2.2)	6 (1.5)	14 (3.1)	10 (2.1)	9 (2.3)	6 (1.8)	12 (2.4)	87 (2.2)
LTFU	160 (27.7)	24 (5.3)	7 (2.0)	5 (1.2)	13 (2.9)	19 (4.1)	7 (1.8)	11 (3.2)	10 (2.0)	256 (6.5)
Not evaluated	75 (13.0)	75 (16.7)	16 (4.5)	18 (4.5)	19 (4.3)	15 (3.2)	9 (2.3)	11 (3.2)	34 (6.9)	272 (6.9)

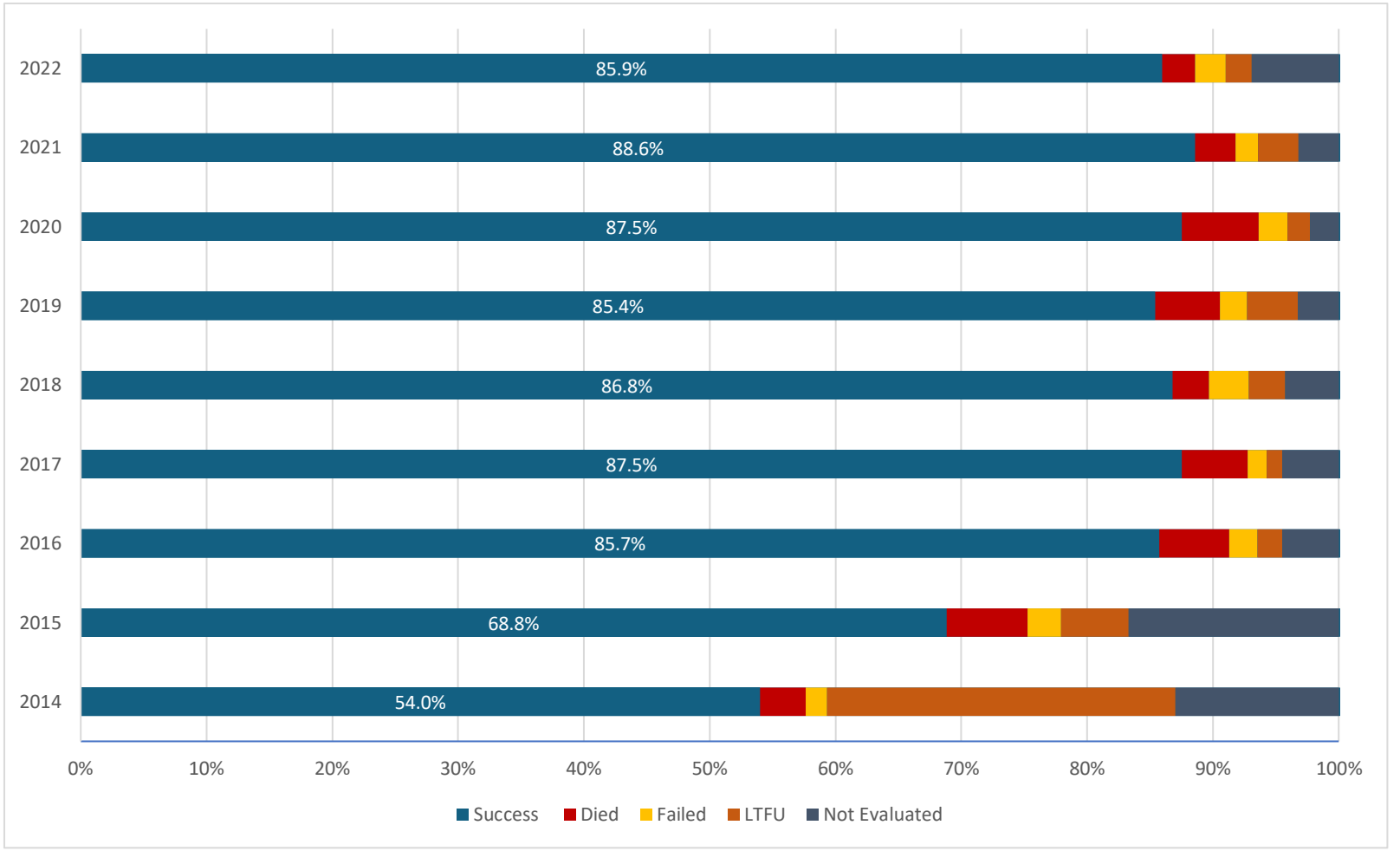
LTFU: lost to follow-up

Table 3.4 Treatment outcomes for people with MDR/RR-TB, South Fly District, 2014–2022

	2014 n (%)	2015 n (%)	2016 n (%)	2017 n (%)	2018 n (%)	2019 n (%)	2020 n (%)	2021 n (%)	Total n (%)
Favourable	54 (68.8)	92 (78.6)	106 (88.3)	92 (80.0)	90 (88.2)	94 (83.2)	112 (88.2)	84 (82.4)	3,435 (79.7)
Completed	30 (38.0)	76 (65.0)	71 (59.2)	75 (65.2)	60 (58.8)	52 (46.0)	81 (63.8)	72 (70.6)	2,449 (56.8)
Cure	24 (30.4)	16 (13.7)	35 (29.2)	17 (14.8)	30 (29.4)	42 (37.2)	31 (24.4)	12 (11.8)	620 (14.4)
Unfavourable	25 (31.6)	25 (21.4)	14 (11.7)	23 (20.0)	12 (11.8)	19 (16.8)	15 (11.8)	18 (17.6)	873 (20.3)
Died	7 (8.9)	13 (11.1)	11 (9.2)	13 (11.3)	8 (7.8)	14 (12.4)	7 (5.5)	6 (5.9)	242 (5.6)
Failed	2 (2.5)	4 (3.4)	0 (0.0)	4 (3.5)	1 (1.0)	2 (1.8)	1 (0.8)	0 (0.0)	89 (2.1)
LTFU	14 (17.7)	5 (4.3)	3 (2.5)	5 (4.3)	3 (2.9)	2 (1.8)	7 (5.5)	8 (7.8)	293 (6.8)
Not evaluated	2 (2.5)	3 (2.6)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)	0 (0.0)	4 (3.9)	249 (5.8)

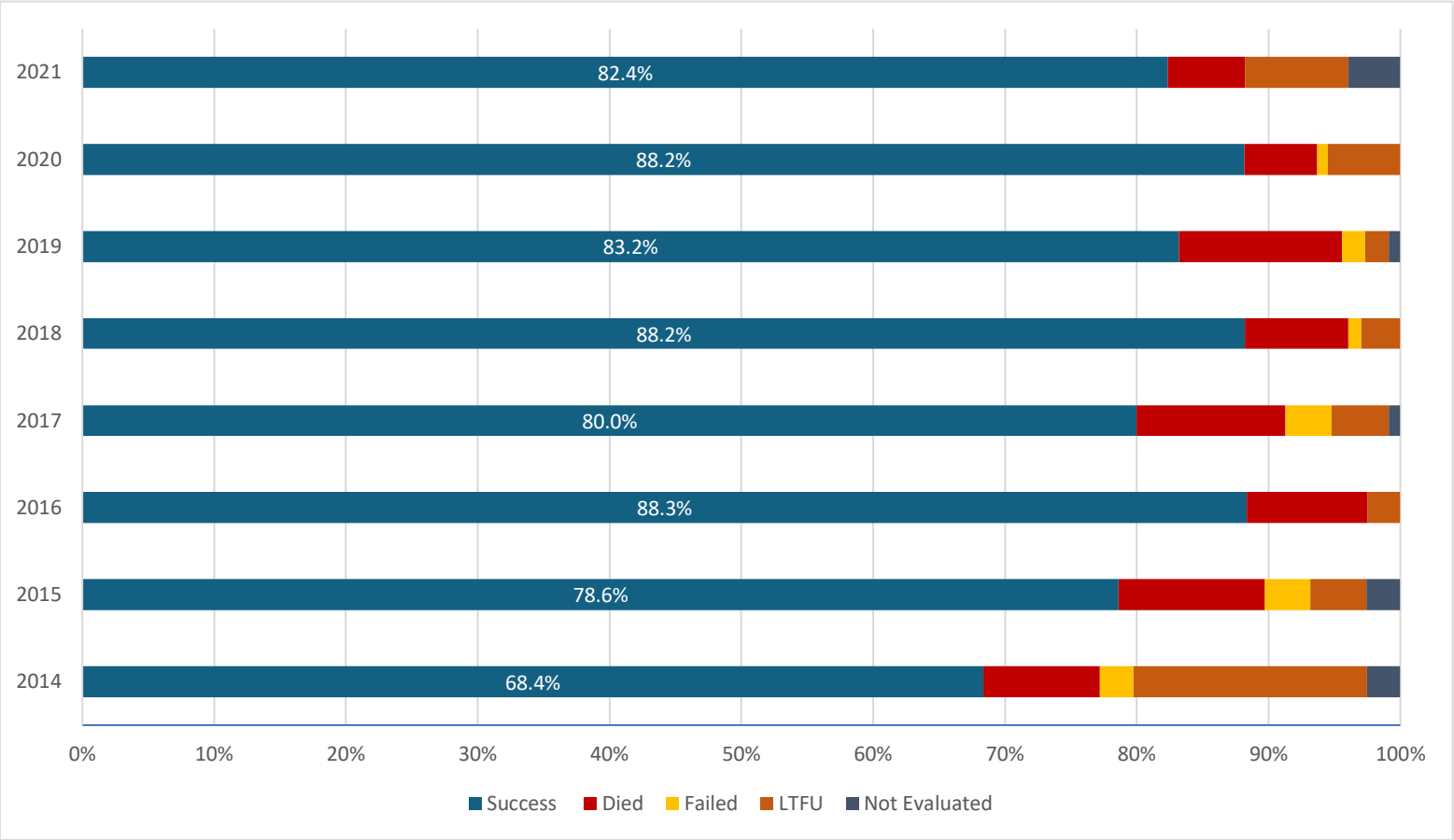
LTFU: lost to follow-up

Figure 3.5 Treatment outcomes for people with DS-TB, South Fly District, 2014 – 2022



LTFU: lost to follow-up

Figure 3.6 Treatment outcomes for people with MDR/RR-TB, South Fly District, 2014–2021



LTFU: lost to follow-up

Figure 3.7 Treatment outcomes for people with TB, South Fly District, 2014–2021

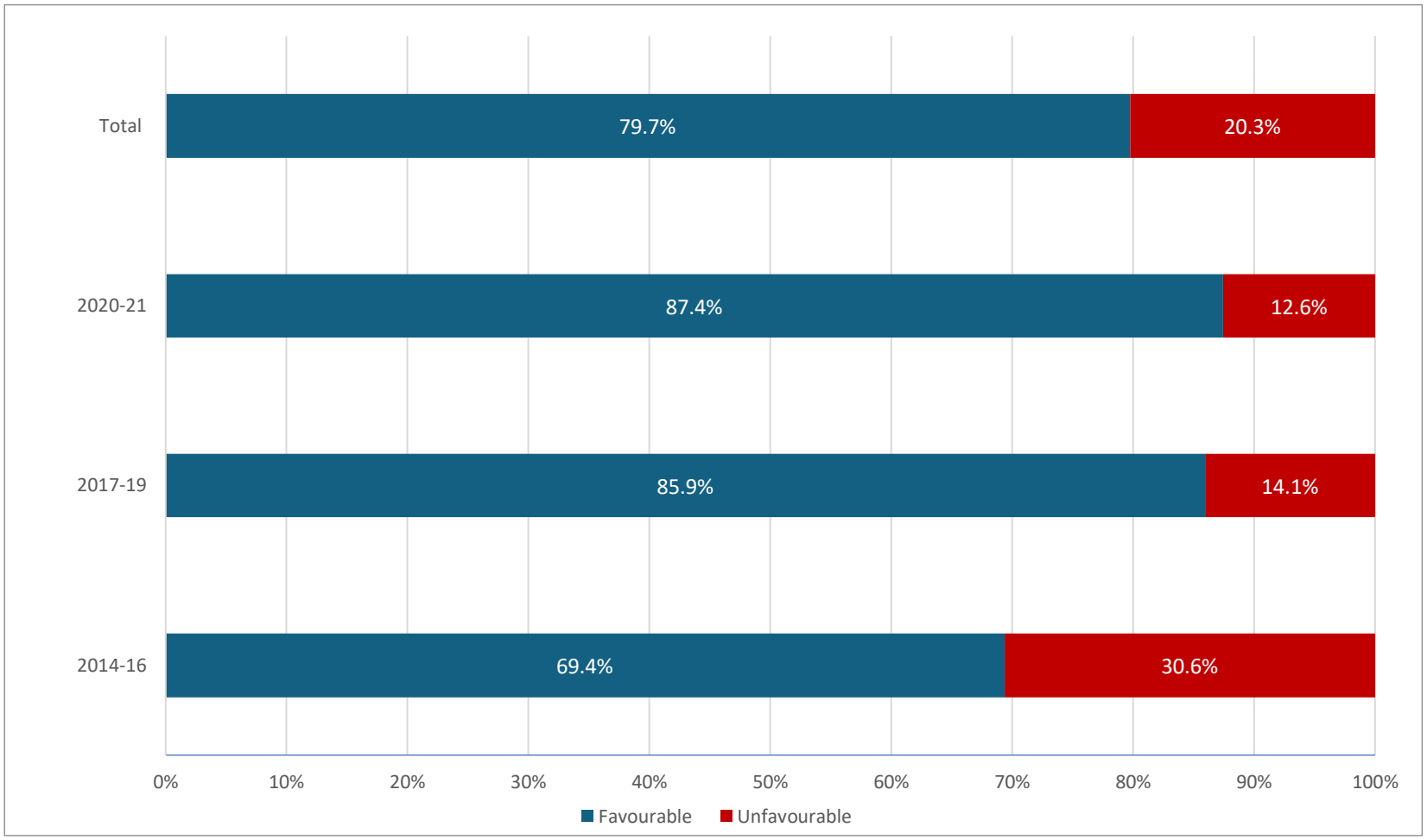


Table 3.5 Factors associated with unfavourable outcomes for people treated for TB, South Fly District, 2016- 2022

Characteristic		Total n (%)	Unfavourable outcome n (%)	OR (95%CI)	p-value	aOR (95%CI)	p-value
Age Group							
	0-4 years	290 (8.0)	40 (13.8)	0.64 (0.43–0.97)	0.035	0.37 (0.21–0.66)	<0.001
	5-14 years	468 (12.9)	40 (8.5)	0.36 (0.24–0.54)	<0.001	0.34 (0.21–0.56)	<0.001
	15-34 years	1,705 (46.9)	260 (15.2)	0.66 (0.52–0.83)	<0.001	0.80 (0.62–1.05)	0.105
	35-54 years	910 (25.0)	190 (20.9)	Reference		Reference	
	≥55 years	260 (7.2)	70 (26.9)	1.43 (1.01–2.02)	0.042	1.11 (0.73–1.70)	0.619
	Unknown	3 (0.1)	0 (0.0)				
Sex							
	Female	1,712 (47.1)	262 (15.3)	Reference		Reference	
	Male	1,924 (52.9)	341 (17.7)	1.43 (1.1-1.74)	0.001	1.59 (1.26-2.02)	<0.001
Residence	Daru	2,465 (67.8)	363 (13.5)	Reference		Reference	
	Outside Daru	1,077 (29.6)	217 (20.1)	1.80 (1.48–2.23)	<0.001	1.80 (1.42-2.28)	<0.001
	Unknown	94 (2.6)	13 (13.8)				
HIV Status	Negative	3,186 (87.6)	443 (13.9)	Reference		Reference	
	Positive	81 (2.2)	23 (28.4)	3.11 (1.88–5.14)	<0.001	2.42 (1.39–4.19)	0.002
	Unknown	369 (10.1)	96 (26.0)				
Treatment history	New	3203 (88.1)	451 (14.1)	Reference		Reference	
	Previously treated	413 (11.4)	107 (25.9)	1.89 (1.44–2.48)	<0.001	1.42 (0.99–2.02)	0.056
	Unknown	20 (0.6)	4 (20.0)				

Characteristic		Total n (%)	Unfavourable outcome n (%)	OR (95%CI)	p-value	aOR (95%CI)	p-value
Disease Site	Pulmonary	2320 (63.8%)	347 (15.0%)	Reference		Reference	
	Extrapulmonary TB	1315 (36.2%)	215 (16.3%)	0.84 (0.68–1.03)	0.08	0.88 (0.67–1.17)	0.383
	Unknown	1 (0.0%)	0 (0.0%)				
Diagnosis method	Bacteriologically Confirmed	2428 (66.8%)	321 (13.2%)	Reference		Reference	
	Clinically Diagnosed	1200 (33.0%)	239 (19.9%)	2.13 (1.75–2.61)	<0.001	2.44 (1.83–3.24)	<0.001
	Unknown	8 (0.2%)	2 (25.0%)				
Resistance	Drug Susceptible TB	2902 (79.8%)	390 (13.4%)	Reference		Reference	
	Drug Resistant TB	734 (20.2%)	172 (23.4%)	1.24 (0.97–1.57)	0.088	1.44 (1.05–1.96)	0.022
	Unknown						

OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval

Total sample size for regression analysis = 3,636

Reference groups: 35-54 years (age), female (sex), Daru (residence), HIV negative, new treatment, pulmonary TB, bacteriologically confirmed, drug-susceptible TB

Table 3.6 TB programmatic interventions, South Fly District, 2011-2022

	Baseline (2011-2013)	**Emergency Response (2014 – 2016)**	**Service Strengthening (2017 – 2019)**	**COVID (2020 – 2022)**
Model of care	DOTS Microscopy No active case finding or TPT	Model of MDR-TB care and treatment Xpert as frontline test Peer counselling + education Contact investigation started	Expansion of new MDR drugs Standardised PEC model Child TB strengthening Contact investigation and TPT Systematic screening BCG strengthened	Scaled back to essential treatment and care No active case finding COVID integration
Health Systems	AusAID funding from 2012 WPHA & DPH separation Cross border treatment of MDR-TB 7 TB Staff	Increased donor funding Coordination via WPHO & ERT Provincial strategy and AIP 17 staff + technical partners Strengthened lab, supply and data (EMRS) systems	Research funding (BI) National and provincial coordination, partner meetings PHA established 2019 Workforce strengthening EMRS	No reduction in funding Transition to WPHA caused disruption to coordination HR gaps, fellowship started TB program HR structure Significant stockouts
Community Systems	Advocacy and social mobilisation activity	TB patient representatives Community stakeholder alliance in Daru Training on community-based care	Community engagement training Needs assessments and consultations	COVID integration and vaccination support Community advisory group formed
Data Utilisation	Routine reporting to NTP with gaps	Routine reporting Quality improvement approach Operational research agenda and training plan	Analytic dashboards and cascades SORT-IT conducted CI and IPT implementation study Qualitative research	Weekly process indicators continued 2nd SORTIT course SWEEP-TB planning
Decentralisation	Torres Strait until 2012 Sea ambulance Rural patrols for primary care	Systematic outreach services 1 decentralised MDR-TB care site	Plan with 2 sites Facility construction New partners (aviation patrols)	Limited progress Border closed

DOTS: directly observed treatment, short-course; PEC: patient education and counselling; BCG: bacille Calmette-Guérin; AusAID: Australian Agency for International Development; WPHA: Western Provincial Health Authority; DPH: Daru Provincial Hospital; WPHO: Western Provincial Health Office; ERT: Emergency Response Team; AIP: Annual Implementation Plan; EMRS: electronic medical record system; BI: Burnet Institute; HR: human resources; NTP: National Tuberculosis Program; SORT-IT: Structured Operational Research Training Initiative; CI: contact investigation; IPT: isoniazid preventive treatment

3.4 Discussion

TB case notifications are very high in SFD with alarming levels of incident TB in Daru residents. The CNRs of TB and MDR/RR-TB in SFD of 638 per 100,000 and 122 per 100,000 are some of the highest reported at a subnational level, particularly in a setting with low HIV prevalence. The Daru-specific CNR of 1,815 is alarming, and analysis of data indicates intense TB transmission. This is compounded by a very high level of MDR/RR-TB (32.1% of all bacteriologically confirmed TB in SFD) that is transmitting efficiently with 61% people with MDR/RR-TB reporting no previous treatment. The emergency response from 2014 to 2016 resulted in the rapid establishment of a comprehensive programmatic response to TB with improvements in treatment outcomes for DS and MDR/RR-TB and rapid reduction in high rates of LTFU. The service strengthening period from 2017 to 2019 showed stabilisation of case notification trends with a reduction in DS-TB and increase in MDR/RR-TB and continued improvements in program performance, systems and model of care development. During the COVID period (2020 to 2022) decreased case detection with recovery in 2022 and minimal disruption to TB treatment outcomes was seen, likely demonstrating resilience in the systems despite the challenges. These are important findings and successes for a remote setting in PNG, and for a high transmission MDR/RR-TB setting where a community-based model of care for TB was developed. Significant challenges were identified across all periods as progress was slower than anticipated in a very fragile health system that was compounded by a very high TB burden.

3.4.1 TB epidemiology

PNG and global context

The combination of a very high burden of MDR/RR-TB in SFD and Daru in a relatively small, remote population makes SFD's situation unique in PNG and globally. A TB prevalence survey has not been conducted in PNG, however, community-based screening conducted in Daru in 2018 using CXR and Xpert MTB/RIF demonstrated a TB prevalence of 853 per 100,000 among those screened (n=8,085).[151] This is lower than the CNR in Daru found in this study and may be an underestimate due to the low uptake of screening (42.9% of eligible). Furthermore, the screening may have had a low coverage among those at risk of TB as it used a fixed-point site (i.e. not household) and excluded children under 10 and people who could not travel to the site.

The TB and MDR/TB CNRs in SFD are substantially higher than the national CNRs of 393 per 100,000 for TB and 21 per 100,000 for MDR/RR-TB reported in 2023.[1] In PNG MDR/RR-TB comprised 2.8% of all bacteriologically confirmed pulmonary TB in 2023 and 4% of new cases and 23% among previously treated cases in 2021.[1,406] The available epidemiological data in PNG indicates that there is a widespread national TB epidemic with a heterogeneous distribution of drug-resistance.[144,407] There were only three provinces with a higher CNR than SFD in 2016 – Gulf (669), West New Britain (907) and NCD (1,117).[406] A drug-resistance survey conducted from 2012 to 2014 with a limited sample of 1,182 patients from four provinces found that 37% were from the NCD and 34% from Daru detected MDR-TB in 2.7% of new and 19.1% of previously treated patients.[408]. These two geographic locations have since accounted for most MDR/RR-TB notifications and were the hotspots of focus for the emergency response. A review of laboratory samples from the national reference laboratory from 2012 to 2017 (n=770) found that 33.9% of MDR/RR-TB were from Daru and 42.6% were from the NCD.[144] MDR/RR-TB was detected in 9.3% of people with TB in Port Moresby General Hospital from 2018 to 2022 (n=1,027).[409]

South Fly District reports one of the world's highest burdens of MDR/RR-TB, measured by both case notification rates and proportion of drug-resistant cases. While it has been standard WHO surveillance to report the proportion of MDR/RR-TB among new cases to understand 'primary transmission,' this may be an underestimate as previously treated cases of DS-TB may actually have reinfection with an MDR/RR-TB strain.[410] Therefore, proportions may underestimate the extent of community transmission and population estimates may be more accurate in geographical settings.[411] However, comparisons with other sub-national regions based on CNR should be interpreted cautiously if there is uncertainty on case detection or population estimates. Globally, in 2023 the estimated proportion MDR/RR-TB was 3.2% (95% UI: 2.5–3.8%) in new cases and 16% (95% UI: 9.0–24%) in previously treated cases.[1] The countries with the highest proportions of people with TB who had MDR/RR-TB (>20% of new and >50% of previously treated cases in 2023) were the Russian Federation and in several countries in Eastern Europe and Central Asia.[1] The estimated MDR-TB incidence in these countries ranged between 5 and 35 per 100,000, compared with 122 in SFD.

Globally, at a subnational level, several MDR/RR-TB hotspots have been reported in urban settings. A drug-resistance survey in Mumbai conducted from 2004 to 2007 reported MDR-TB in 24% of new and 41% of previously treated cases.[412] A large slum area in Mumbai, Dharavi (population of 1 million), has an estimated CNR for MDR-TB of

30 per 100,000 people which increased with migration during the COVID-10 pandemic to 75-100 per 100,000.[413] Khayelitsha, an urban township in South Africa (population of 500,000) has an estimated a MDR-TB CNR of 55 per 100,000 (in 2009-2011).[414,415]

In more remote settings, there has been limited availability of DR-TB diagnostics and surveillance with reports from several dedicated MDR-TB projects. In Central Asia, a sub-national cross-sectional TB resistance survey in Turkmenistan and Uzbekistan (n=213) conducted in 2002 showed MDR-TB in 26.8% of all pulmonary smear-positive TB, and in 13.2% of new and 40.2% of previously treated cases.[416] A MDR-TB program in a former Soviet Union region (Abkhazia, population ~200,000), showed MDR-TB in 18% of all TB, and an estimated MDR-TB CNR of 30 per 100,000.[417]

South Fly District has the highest rate of TB and MDR-TB reported from the Pacific region. Pacific Island countries (PICs) have an estimated TB incidence of 69 per 100,000 in 2020, with substantial variation.[418] The Marshal Islands and Kiribati have similar incidence to PNG of 483 and 425 per 100,000, respectively. PICs have reported small numbers of MDR/RR-TB, with only 52 notifications from 15 countries in the period 2015 to 2019.[418] Micronesia has reported an MDR-TB outbreak from 2007 to 2009 with five cases, of whom four died, in Chuuk State (population 55,000), that has a TB CNR of 127 per 100,000.[419]

Characteristics of people with TB

The key epidemiological features of people who were treated for TB in SFD were a young population (median age of 25 years) with predominance in the 15-34 years age group, only slightly more males than females, a low rate of HIV co-infection, a relatively high bacteriological confirmation rate and moderately high level of extrapulmonary TB. This age distribution, proportion of new cases and proportion of extrapulmonary TB is similar to national data and reports from other provinces in PNG.[406,407,420–423]

The near-parity in TB notifications between males and females (M:F ratio 1.04:1) in SFD is notable, as male notifications typically substantially outnumber female notifications in PNG (M:F ratio 1.2:1) and globally (M:F ratio 1.7:1).[1,142] The reasons for this are not entirely clear but likely reflect the very high levels of TB where widespread community TB transmission confers similar elevated exposure risk to both sexes. Active case-finding strategies, including household contact investigation, may have also contributed to more equitable detection. Despite similar notification rates, males had significantly worse

treatment outcomes, suggesting persistent sex-based disparities in health service access, utilisation, or treatment adherence.

The rates of HIV-TB co-infection vary throughout PNG which has an HIV epidemic concentrated in key populations and the Highlands regions.[424] However, in SFD, the rate of bacteriologically confirmed TB was markedly higher than most provinces (22% to 38%) and nationally (15.6% and 25.9% among pulmonary cases from 2008-16). These findings reflect better access to and utilisation of TB diagnostics in Daru due to the earlier availability of Xpert MTB/RIF than in other provinces.[144]

The age group with the highest TB case notifications in PICs and the Western Pacific region are adults aged over 55 years.[418] This difference most likely reflects less intense community TB transmission in PICs and/or better TB control than PNG and SFD. It may also reflect a cohort effect (greater historical exposure in older adults) and/or a greater life expectancy in PICs compared with PNG.[56,142] The proportion of extrapulmonary among all TB in PICs are 29% and it is lower, 16%, globally.[1,418] The higher rates of extrapulmonary TB in PNG and SFD, which is not often seen in HIV-uninfected populations reflects a higher TB burden in children and adolescents, who are more likely to have extrapulmonary TB or less, likely, be explained by host factors (delayed diagnosis and dissemination or malnutrition which lowers immunity).[425] It could also potentially be due to over-diagnosis, but the fact that the proportion remained stable with improved diagnostic capacity over time suggests it may reflect true disease patterns.

TB and MDR-TB transmission in SFD

The findings in SFD of a high proportion of TB cases registered as new (86.1%), a high proportion of TB in children (20.7%) and a high proportion of MDR/RR-TB cases among all TB and a high proportion people with MDR/RR-TB reporting no previous treatment, indicate there are high levels of community TB transmission, including for MDR/RR-TB. The high proportion of people with TB who identified as Daru residents indicates that the island is likely to be the focus of transmission. However, there may be under detection of TB in SFD outside of Daru, who did not have access to TB services.

This epidemiological pattern must be understood in the context of the social and structural determinants that create ideal conditions for TB transmission on Daru.[71] First, severe overcrowding in informal settlements is a critical factor with multigenerational kinship groups (family structures) sharing crowded and adjoining dwellings, with extended contact.[94,152] This, combined with the mobile nature of the population, with

people moving between Daru and mainland villages for services and economic opportunities, may facilitate spread beyond the island where there are limited TB detection and treatment services and contribute to more transmission. Second, significant and widespread poverty affects both exposure risk and healthcare seeking and utilisation.[137] Third, food insecurity and resulting undernutrition are another key drivers of TB risk.[390] Previous qualitative research in Daru has highlighted how economic constraints force families to prioritise basic needs over healthcare, leading to delayed diagnosis.[152,153] These factors combined create a perfect storm for TB transmission-increased exposure risk in confined spaces coupled with compromised host immunity.

A molecular epidemiology study of 100 MDR/RR-TB samples from DPH confirmed this epidemiology and demonstrated that drug-resistance is primarily transmitted in the community, rather than acquired from incomplete DS-TB treatment.[148] The study showed a modern Beijing sub-lineage MDR/RR-TB strain with a long evolutionary history after emerging in the 1990s and 4 circulating clades. A dominant clade accounted for 95% of strains and had a unique resistance profile which correlated with phenotypic resistance. XDR-TB was shown to have emerged more recently (around 2008 to 2009) which corresponds with the introduction of MDR/RR-TB treatment. A second molecular epidemiology study of additional samples from across PNG provides lines of evidence that the MDR/RR-TB strain emerged in the NCD and spread to Daru where intense transmission, or a major outbreak occurred, and to other parts of PNG which did not see outbreaks.[143] A third study demonstrated the Daru MDR/RR-TB strain in PNG residents of the Torres Strait Protected Zone, a potential hotspot of transmission outside of Daru in the coastal village of Mabudawan and transmission to Australian citizens across the border.[426] Beijing genotype strains are associated with an increased risk of unfavourable treatment outcomes.[427] Taken together, this suggests that once drug-resistant strains are introduced into these high-risk environments, such as Daru, they can spread efficiently through the population and sustain transmission, despite good treatment outcomes.

3.4.2 TB and MDR/RR-TB treatment outcomes

The treatment success rates (favourable outcomes) for all TB in SFD increased during the emergency response and were maintained throughout the study period: increasing from 65% in 2014 to 88% in 2021. This is comparable to the current global TB treatment success rates for DS-TB of 88% for the 2022 cohort and markedly better than that for MDR/RR-TB, 68% in 2021.[1] The proportion of unfavourable outcomes in SFD (20.3%)

was lower than PICs (26% in new and relapse) and other reported provinces in PNG (35 to 45%).[407,418] Furthermore, unfavourable outcomes were slightly better in SFD than for patients presenting to Australian health facilities in the Torres Strait (26%) from 2013-2020.[428]

The proportion (17.6%) of unfavourable MDR/RR-TB outcomes in SFD was lower than or comparable to several similar community-based programs LMICs or settings during the same time-period–50% in NCD,[409] 44% in Uzbekistan,[429] and 15 to 30% in Khayelitsha, South Africa.[430]

Several key factors may have contributed to this success. First, SFD was an early adopter of more effective MDR/RR-TB treatment regimens. The program systematically introduced bedaquiline-containing, all-oral regimens from 2015, well ahead of global policy changes and drove changes in PNG national guidelines in 2017.[149] This regimen has better tolerability and success compared with older injectable agent based regimens.[149,431] The program also benefited from detailed molecular epidemiology data that informed regimen design-understanding the unique resistance patterns of the dominant Beijing strain allowed optimisation of drug combinations. Unlike many settings that use standardised regimens, this evidence-based approach likely contributed to better outcomes.

Second, the development of a person-centred, community-based model of care. While many programs struggle with high loss to follow-up due to centralised care models, SFD achieved a dramatic reduction in LTFU from 30.7% to consistently below 5% through decentralised treatment sites on Daru, a dedicated TB case manager for patient care and the program's patient support package - including daily meals, transport assistance, and dedicated peer counselling. These patient-centred interventions addressed structural barriers that often lead to treatment interruption. Qualitative research in Daru conducted in Chapter 4, and a subsequent study has highlighted that these structural supports were potentially more important than addressing knowledge gaps or stigma and has highlighted the value of the peer counsellor model.[153] This experience is similar, but perhaps more comprehensive than a community-based MDR/RR-TB treatment program in South Africa which demonstrated the importance of patient-centred care and supports.[430] The small geographic size of Daru also facilitated implementation of community-based care in ways that might be more difficult in larger urban settings or more dispersed rural populations.

Third, the program benefited from sustained technical assistance and partnership support that enabled expert advice, capacity development and continuous quality improvement. Unlike many programs that receive short-term or intermittent external support, the WPHA maintained long-term partnerships in SFD that allowed for capacity building, clinical mentoring, and systematic strengthening of programmatic systems. The introduction of real-time monitoring of a cascade-of-care approach to monitor retention and an EMRS for cohort monitoring and enabled rapid feedback and program adaptation. The emergency response created a strong foundation through intensive investment in laboratory systems, clinical protocols, and workforce capacity. The sustained political commitment and resource mobilisation, though initially driven by outbreak concerns, enabled the development of robust systems that could be maintained through subsequent phases. However, it's important to note that these successes came with significant resource requirements and intensive support that may be challenging to replicate in other settings.

The persistent death rates, 5.6% overall, despite marked improvements in treatment success rates, warrant deeper analysis. Several factors may contribute to this concerning finding. First, delayed diagnosis and treatment initiation may be significant factor, particularly for MDR/RR-TB. Previous research at DPH in 2017 demonstrated that MDR/RR-TB was associated with delayed treatment initiation (>7 days post-diagnosis), consistent with evidence from other settings where diagnostic delays increase mortality risk. [432,433] The higher death rate in MDR/RR-TB patients (9% vs 4.5% for DS-TB) may reflect both these delays and the greater complexity of their disease. Second, clinical factors may play an important role. While the study could not systematically capture data on nutritional status, co-morbidities, or disease severity at presentation, these are well-established risk factors for TB mortality.[434] The socioeconomic conditions in Daru, particularly food insecurity and overcrowded housing, likely contribute to poor nutritional status and advanced disease at presentation. The Beijing genotype strain dominant in Daru has been associated with more severe disease and poorer outcomes in other settings, which may compound these factors. [427] Third, health system factors may contribute with gaps in early detection of TB, particularly active case finding and access to services outside of Daru. There may also be gaps in clinical care and management at DPH that may affect survival for the most severely ill patients.

Factors associated with Unfavourable Outcomes

In the logistic regression analysis, the characteristics associated with unfavourable outcomes–male gender, living outside Daru, being clinically diagnosed, MDR/RR-TB and

HIV-positive status-were consistent with the global literature. Younger age (children <14 years) was protective against unfavourable outcomes. This could be explained by good access and utilisation of TB services through parental support. While childhood TB remains a major global health challenge, children who are treated for TB, including young children and those with MDR/RR-TB, have low mortality and favourable outcomes.[435,436] MDR/RR-TB is a well-established risk factor for poor TB outcomes compared with DS-TB given the potential delays in diagnosis and less effective and tolerable treatment.[437] The effect of HIV was less than seen in other settings, such as sub-Saharan Africa, noting the HIV cohort in SFD was small and HIV management may have been better.[438,439]

Globally, males have a higher rate of TB notifications and worse treatment outcomes. The reasons for these differences have not been investigated locally or mechanistically established. These differences may be due to biological sex differences or environmental factors such as alcohol, smoking or substance use, co-morbidities or engagement in care.[1,440] Analysis of risk factors among people diagnosed with TB following community screening in Daru in 2018 showed that around 50% were smokers, 38% used alcohol and the majority (74%) had very low household income (< US$50 per month).[151] However, these factors were not statistically associated with TB in this previous analysis. Remoteness, or living outside Daru is a major barrier to effective utilisation of TB and health services in SFD. There is limited decentralisation of TB services, particularly for MDR/RR-TB, therefore, patients from villages farther way often have to choose between relocation or returning home and their livelihoods.[152,153] The association of clinically diagnosed TB and unfavourable outcomes could be due to (1)clinically diagnosed TB resulting in clinically worse outcomes, such as TB meningitis, and therefore death (2)overdiagnosis of TB in patients with other conditions that increase risk of death or LTFU or (3)more likely, patients may have no or minimal symptoms (e.g. TB lymphadenitis or clinically diagnosed pulmonary TB) and may not complete treatment if there is improvement or adverse effects from treatment. A more detailed investigation of clinically diagnosed TB is warranted through clinical audit.

Operational research from other provinces in PNG has identified similar factors associated with unfavourable outcomes–clinically diagnosed TB, pulmonary TB, older age, living remotely/distance to TB services and MDR/RR-TB.[409,420–423] Co-morbidities were associated with unfavourable TB outcomes among patients who presented to Australian clinics in the Torres Strait.[428]

3.4.3 The Impact of programmatic interventions and COVID-19

Emergency Response and Systems Strengthening phases

The programmatic description demonstrates an emergency response focussed on the rapid establishment of a comprehensive response to TB that established a functional model of care for the detection, treatment and prevention of TB, while addressing the underpinning health systems requirements for the delivery of TB services. The response can be characterised by the confluence of high-level political commitment; mobilisation of additional funding and resources to implement the provincial response plan; and collaboration between technical assistance partners under the leadership of provincial and national health authorities.[147,404] The high-level political commitment and governance reforms were foundational. The formation of the Emergency Response Taskforce under NDoH leadership in 2014 provided crucial oversight and coordination of the multi-stakeholder response. This created clearer lines of accountability and fast-tracked decision-making and solutions to health systems bottlenecks (e.g., drug procurement, laboratory systems). The establishment of the Provincial TB Core Group and implementation team meetings ensured local ownership and coordination. This governance structure was particularly effective because it balanced national oversight with local autonomy in implementation and provided input for technical partners.

Perhaps most critical was the development of joint planning between national and provincial governments, facilitated by the technical partners. This enabled a locally led approach and resource alignment from donor partners. The rapid mobilisation of increased resources in 2014 by the Australian Government was critical and enabled immediate strengthening of essential components-diagnostic capacity, drug supply, clinical expertise, and community engagement. Unlike many emergency responses that focus solely on immediate clinical needs, SFD's response invested significantly in health systems strengthening from the outset and longer-term capacity building. The technical assistance model was particularly effective. Rather than relying on short-term external consultants, the program established long-term partnerships with a technical agency that provided sustained clinical and programmatic mentoring. This allowed for continuous capacity building and system strengthening while maintaining service delivery.

The response during the study period focused on detection and treatment of TB and strengthening facility and community-based systems with introduction of diagnostic and treatment strategies that brought the program into line with the evolving WHO guidelines, particularly for MDR/RR-TB, when PNG guidelines had not advanced. This included Xpert as the frontline test, use of C-DST for monitoring, strengthening MDR/RR-TB

treatment regimens, providing patient centred care and support, the initiation of contact investigation and TPT (see Chapter 5**)** and enhanced data utilisation for action. The establishment of an electronic medical record system for TB was key in strengthening clinical management, TB program monitoring and evaluation and operational research, including the introduction of new TB drugs with active drug safety monitoring.[149] The TB program in Daru was seen as a 'national centre of excellence' and trained health workers and managers in TB and supported an operational research capacity building initiative for healthcare leaders and staff from other provinces.[158]

The successful treatment outcomes achieved were associated with the development and increasing evolution of community engagement strategies which are recognised as central to effective programs.[441] The program moved beyond traditional health education approaches to develop a comprehensive community engagement model that recognised the complex social and cultural context of TB in Daru. The formation of the TB patient representative group and Community Advisory Group (CAG) provided critical mechanisms for community input into program design and implementation. This helped shift the program from a facility-centred to a community-based approach that was more responsive to local needs and challenges. The peer counselling program, which engaged TB survivors as educators and patient supporters, proved particularly effective.[150,154] Their role extended beyond adherence support to include advocacy, stigma reduction, and strengthening community trust in TB services.

However, there were also limitations in the emergency response that continued in the later phases. There was limited progress on decentralisation beyond Daru due to the significant additional resources required in a such a remote setting. There were challenges in establishing sustainable human resource structures and there was turnover of senior WPHA leadership.

The successful development of a community-based model of care in SFD, while ultimately achieving impressive outcomes, faced several significant challenges and yielded important lessons. The evolution from a traditional facility-based model to decentralised, patient-centred care required substantial adaptation to local contexts and continuous refinement based on implementation experience. There as initial resistance from some clinical staff accustomed to hospital-based care and from the community, which was managed through engagement. Sustaining human resources remained an ongoing challenge. There was high turnover of hospital and community health workers, with long gaps in local clinicians that were substituted by international staff. Maintaining

motivation of treatment supports with limited compensation was a challenge. Key lessons were the need to develop person-centred strategies, and beyond community engagement, co-designing with communities. This was achieved through establishment of the CAG.

The TB CNR trends show sustained high levels of TB transmission over the nine years from 2014, even with significant strengthening of TB detection, treatment and systems from baseline as evidenced by the very good treatment outcomes. This indicates that current interventions are insufficient to interrupt TB transmission in Daru and SFD. A community-based population screening initiative in Daru in 2018 detected 69 people with TB or 0.85% of those screened, among a total of 397 people with bacteriologically confirmed TB notified during the implementation period.[151] Methods for evaluation of attribution and/or additionality of case detection to the intervention in observational studies have limitations.[442] However, despite this direct yield from screening, this active case finding intervention did not result in a subsequent decline in TB case notifications or a change from baseline. A community-based cluster RCT in 60 communities in Vietnam that evaluated active community-wide case finding with annual Xpert MTB/RIF screening (approximately 42,000 participants in each arm) resulted in a 57% reduction in TB incidence over 3 years and a 50% reduction in the prevalence of TB infection in children.[205,207] The coverage of screening in this study was much higher (62% to 78%) compared with Daru (43%), and there were three annual cycles of screening compared to one screening in Daru which was conducted over 12 months.

Responses to outbreaks of MDR/RR-TB in Micronesia, in Tugela Ferry in South Africa and in developed countries have demonstrated that MDR/RR-TB and even XDR-TB outbreaks can be rapidly controlled if there is a concerted effort by governments who have high levels of political commitment coupled with support from multiple national and international agencies.[81,443,444] These responses highlight the possibility of further reducing the burden of TB in Daru by utilising comprehensive approaches that include patient-centred care and community-based case finding and preventive treatment, including for MDR/RR-TB.[7,36,129,174] The next phase of intervention in Daru and SFD focused on reducing TB transmission through community wide screening, detection, treatment with the addition of community-based prevention for TB and MDR/RR-TB (Chapters 6, 7).[94]

COVID-19 impacts

TB case detection declined by 29% in 2021 compared to pre-COVID, with recovery in 2022. Despite COVID-related disruptions to TB services, successful TB treatment outcomes were maintained. The interventions and resources directed towards TB and health systems strengthening in Daru and SFD since 2015 have likely contributed to this and may have included-the formation of effective and sustained partnerships and enabling governance mechanisms; the availability of technical assistance during the pandemic; a focus on community engagement, training and development of capacity in the community and health workforce; the implementation of standardised procedures for facility- and community-based TB and MDR/RR-TB care; and a focus on data management through electronic reporting and data utilisation to inform decision-making.

Unlike many settings where data systems collapsed during COVID-19, the EMRS enabled real-time patient monitoring through weekly process indicators, even with reduced staff. Clinical management and technical assistance were provided through remote support and training was moved online, despite challenges with internet connectivity. Community treatment sites remained functional during COVID-19 disruptions, and treatment supporters and counsellors maintained patient contact when facility access was limited. Flexible medication delivery systems adapted to longer take-home periods. Task-shifting to community health workers and peer counsellors enabled service continuation despite staff shortages. The integration of TB and COVID-19 services around a community-based model was successful. Disruptions were seen in key health system components with human resource shortages, laboratory capacity and testing gaps and drug stockouts.

The increase in bacteriological confirmation during COVID-19 demonstrates that laboratory diagnostic services remained functional with a likely reduction in the clinical diagnosis of TB due to human resource shortages. The data from SFD reflect global trends of disruptions to TB services from COVID-19, with an 18% reduction in TB notifications in 2020, partially recovery in 2021 and 2022 levels rebounding to above those in 2019.[91] The Western Pacific had the largest reduction and smallest recovery of all regions. Globally, it was estimated that TB incidence increased by 3.9% from 2020 to 2022 and TB related deaths increased from 2020 to 2021.[91] This reflects the impact of disruptions to access and provision of TB services during the COVID-19 pandemic that led to more undetected TB and increased transmission.

In SFD, COVID-19-related health workforce and health system changes had a major impact on TB services. Active case finding among household contacts was halted, and

community access and utilisation of TB diagnostic services was reduced, despite the limited duration of lockdowns in SFD. The reduction in TB detection noted in young children is consistent with observations elsewhere.[445] This may reflect an increased detection gap because of interruption to facility-based services for clinical diagnosis and to household screening of child contacts. As TB in young children is a sentinel marker for recent community transmission, it may also indicate less exposure to TB during the COVID period, at least outside of the household setting.

Globally, TB treatment success for MDR/RR-TB dropped to 63% in 2020 and increased to 68% in 2021.[91] That treatment outcomes did not fall in SFD, a remote and resource-limited setting, was likely due to the health systems strengthening activities that had occurred since 2015 and the targeting of the reduced resources toward patient care and support–including education, counselling, nutritional support and flexible delivery of care. The peer counselling model that continued during COVID-19 may have been influential–treatment adherence challenges were identified in 43% of 16,234 counselling sessions from 2020 to 2022.[150,446] People on treatment were supplied TB medications to take home (self-administered treatment), including for MDR/RR-TB. The program-initiated process indicators were monitored to track the weekly proportion of patients retained in care and community health worker teams were engaged in follow-up and support. An examination of lessons from TB and COVID-19 response in Brazil, India and South Africa noted key interventions that can be deployed to address both TB and COVID-19 – behavioural prevention methods including mask wearing; screening and contact tracing; digital health technologies; multi-sectoral engagement; and community-led participation.[447]

Operational research from similar low-resource, high-TB burden settings has described the impact of the pandemic. In Malawi and Sierra Leone, there was a reduction in TB case detection and maintenance of successful treatment outcomes during COVID.[448,449] In other settings such as Brazil, Kazakhstan, Mexico and Zimbabwe treatment success decreased during the COVID-19 period to early 2021.[450–453] A health systems strengthening and TB quality improvement project in Mimika District, Papua Province, Indonesia demonstrated greater resilience to COVID-19 impacts than reported nationally.[454] The experience in this remote, high-incidence setting was not dissimilar to our experience across the border in SFD. There was a drop in annual case notifications by 19% but treatment outcomes were maintained, and a rapid “recovery” of detection was noted. A health system strengthening intervention in South African primary health

care clinics demonstrated increased TB testing and detection, compared with control clinics.[455]

3.4.4 Strengths and limitations

A strength of this study is that it provides unique data over a decade on TB detection and treatment with demographic and clinical data in PNG, where TB surveillance systems are weak. Second, data quality and completeness were very good compared with other locations in PNG, the Pacific and similar remote settings due to the implementation of the EMRS, supporting data staff from 2016 and this health information system was not disrupted during COVID. Third, the case detection algorithm was relatively constant for most of the study period with Xpert MTB/RIF used as the initial test for all presumptive TB from 2016 and for smear-positive TB prior to that.

Data completeness for most demographic and clinical variables was excellent (<1% missing). HIV status had 13.7% unknown overall, declining from 38.7% in 2015 to <5% by 2018 as systematic testing protocols were implemented. Treatment outcome ascertainment showed 6.9% 'not evaluated' for DS-TB overall, with higher rates in 2014-2015 (13-17%) improving to <5% from 2016 onwards, and 1.3% for MDR/RR-TB. These systematic temporal patterns of improving data completeness reflect programmatic strengthening during the study period.

There are limitations of this retrospective, observational study. First, the internal validity of the findings related to TB detection as a reliable marker for TB burden (incidence) estimation was limited by the passive case finding model (numerator) and population estimates (denominator). Case notification rates were calculated using the 2021 population as the denominator for all years (2014-2022), the only available population data for South Fly District during this period. Comparing the 2011 census and the 2021 estimate, SFD experienced a 3.62% compound annual growth rate. While retrospective annualised population projections could be applied, this would introduce more unvalidated assumptions about uniform growth patterns. Using the 2021 denominator is a more pragmatic approach that may underestimate the CNR in earlier years (difference of 219 per 100,000 in 2014), meaning the initial TB burden and magnitude of decline during the emergency response period may have been greater than reported. However, this has no impact on the interpretation of temporal patterns or programmatic trends (average difference of 83 per 100,000 across the study period, compared to annualised methods). Further, the substantial cyclical migration to and from Daru and the mainland has not been quantified. In this setting, there are no national identification systems, so

there was potential for reidentification issues and age and residence misclassification, due to patient recall and/or awareness.

Second, inference cannot be made regarding drug-resistance other than MDR/RR-TB, such as isoniazid mono-resistant TB, as DST or molecular tests for isoniazid were only performed on RR-TB. Third, data on key risk factors was not available in the routine surveillance system and would inform a better understanding of TB epidemiology in SFD. This includes collecting information on nutritional status, co-morbidities including diabetes mellitus, smoking and alcohol history and data on education status and socio-economic index. While treatment outcomes improved significantly, there are limited quantitative data to explain which social and behavioural factors influence TB detection and outcomes, and which aspects of patient support were most effective, or what barriers remained unaddressed. This will be explored through analysis of qualitative data in Chapter 4.

Fourth, whilst it was thought that there was limited pre-treatment LTFU, this was not assessed. The data source for the cohort was the TB treatment registers, and the TB laboratory and presumptive TB registers were not entered into the EMRS and were not reliable for analysis. Fifth, the modified operational definition used for treatment failure in MDR/RR-TB (excluding regimen changes when patients were responding to treatment) may have led to underestimation of true failure rates compared to other settings using standard WHO definitions. Sixth, COVID-19 surveillance, and programmatic activities were not as well captured as TB data in SFD, limiting interpretation. Finally, the regression analysis included MDR/RR-TB status as a covariate but did not test interaction terms with other predictors, as exploring effect modification was beyond the analytical scope.

3.5 Conclusion

This analysis of TB detection and treatment outcomes reveals several critical insights about TB control in SFD, PNG. First, there were persistently high levels of TB and MDR/RR-TB case notifications in SFD over the study period with alarming levels in Daru. Several epidemiological factors–high TB burden in children and adolescents, high proportion of new cases among MDR/RR-TB– coupled with previous molecular epidemiology indicate ongoing intense community transmission of DS-TB and more importantly, MDR/RR-TB, despite programmatic interventions. The concentration of TB in Daru residents suggests the island remains a focal point for transmission, which may

be enhanced by the cyclical migration of residents to and from the mainland SFD, where there is limited case detection.

Second, the emergency response, community engagement and subsequent health system strengthening achieved remarkable improvements in treatment outcomes in a fragile setting, with treatment success rates increasing from 53% in 2014 to consistently above 85% from 2016 onwards for both DS-TB and MDR/RR-TB. This success was underpinned by sustained technical assistance and partnership support to the WPHA's TB program that facilitated the following key determinants:

1. The implementation of rapid molecular diagnostics and the introduction of more effective MDR/RR-TB treatment regimens
2. The development of a community-based, patient-centreed model of care including patient support
3. Community partnership and engagement
4. Strengthened data systems and operational research capacity building

Third, the program demonstrated resilience during the COVID-19 pandemic, maintaining treatment outcomes. This resilience can be attributed to the robust health systems strengthening that occurred in the preceding years, though the pandemic's impact on case detection highlights remaining vulnerabilities in the system. There is a need to strengthen health systems as part of TB programs to enhance preparedness for future health threats.[456,457] The experience in SFD demonstrates that meaningful community engagement is not just an adjunct to clinical services but a fundamental component of successful TB control in high-burden settings. Future efforts should consider how to institutionalise and sustain community engagement mechanisms, ensuring they remain responsive to evolving community needs and priorities.

Despite these achievements, several critical challenges persist:

1. Ongoing high rates of community transmission that have not been effectively interrupted
2. A persistent death rate among people treated for TB of 5.6% overall (9% for MDR/RR-TB)
3. Limited decentralisation of TB services beyond Daru

4. Unaddressed social and structural determinants of TB transmission including overcrowding in Daru, poor socio-economic conditions, limited investment in healthcare. This will be explored in Chapter 4.

The experience in SFD demonstrates that implementation of high-quality TB detection and care through community-based approaches coupled with technical assistance and health systems strengthening can achieve impressive programmatic outcomes, even in challenging, remote settings with high MDR/RR-TB burden. However, the findings underscore the urgent need for enhanced interventions to reduce transmission, particularly in Daru. The current investments, including international partner support, have no sustainability when the TB burden is so high. Reduction in TB burden will reduce strain on a very fragile health system. The planned community-wide screening and prevention program (Chapters 5 and 6) represents a critical next step required to meaningfully reduce TB incidence and advance towards TB elimination goals,[94] but must be accompanied by continued health and community systems strengthening,[441] and grounded in an understanding of the socio-ecological determinants of TB for this community (Chapter 4).

Chapter 4: Socio-ecological determinants and care experiences of people with TB in Daru, Papua New Guinea – a qualitative analysis

This chapter presents research conducted in 2018 during the service strengthening phase of the TB response in South Fly District. At this time, the MDR-TB care and treatment model was well-established, including community-based care and peer counselling approaches. The study also coincided with early implementation of TPT for young child contacts and the planning phases of systematic screening in Daru.

I led the protocol development under the supervision of qualitative researchers and obtained ethics approval in 2017. With support from my supervisor, I secured funding through the NHMRC TB-CRE program and mobilised and managed the research team based in Papua New Guinea who collected the data. This chapter presents the first comprehensive analysis of this data, noting that a subsequent and separate larger qualitative study was subsequently conducted in Daru by members of this research team (Jops et al.).

I acknowledge the collaborative research effort: Homiri Dorogori and Darius Arona (research assistants), Camilla Burkot (study qualitative research supervisor), Lucy Morris (WPHA project sponsor), Paul Mason (qualitative research training and supervision), Angela Kelly-Hanku (collaborator), Agnes Mek (collaborator), Stephen Bell (overall qualitative methods and analysis supervision), and Steve Graham (overall supervision).

4.1 Introduction

The emergency response to MDR-TB in SFD established a functional model of care for detection and treatment of TB in Daru (2014-16) and strengthened services and systems (2017-19), including patient-centred care approaches and social supports as detailed in Chapter 3.[150,404] Despite substantial investment and focus on the implementation of new biomedical tools such as newer diagnostics tests and treatments and the establishment of a community-based model of care, the human experiences of TB in this setting were not systematically understood or documented.

A range of factors at individual, family and community levels, as well as the nature of services themselves, influence their accessibility and effectiveness in achieving the desired outcomes for people affected by TB.[68,441] The social and economic burden of TB extends far beyond individual patients, affecting entire households and communities.

The complex interplay between individual agency, family support systems, healthcare services, and broader structural factors remains poorly understood in SFD and Daru. Understanding these socio-cultural influences and broader determinants and their impacts is crucial for developing effective, context-appropriate interventions that address both the biomedical and socio-cultural dimensions of TB.[20]

Previous TB research in PNG has primarily focused on clinical outcomes and programmatic indicators, with limited exploration of patients' lived experiences and the household contexts in which TB treatment occurs.[149,404,407,420,458] Operational research to understand the barriers and enablers to accessing and utilising TB services is crucial for ensuring that the design of models of care is adapted to local contexts and centred in the needs of patients. Qualitative approaches to research can gain important insights into TB programs and services, including the accessibility and acceptability of current policy, services and programs.[68,459] There is a paucity of qualitative research on TB to inform these responses in PNG, particularly in SFD.

This dedicated qualitative research study was therefore designed to explore these gaps through in-depth interviews with people accessing TB treatment**.** This study explores the lived experiences of people with TB who are on treatment in Daru, examining how individuals and families navigate the challenges of seeking care, TB diagnosis and treatment. Using a socio-ecological framework,[460] we investigate the individual, community (family, kinship and community) and institutional influences that shape TB care experiences. By centring the voices and experiences of TB patients and their families, this research aims to provide insights that can inform more responsive and effective TB care and prevention efforts.

4.2 Methods

4.2.1 Aims

For people who access TB services on Daru Island, Western Province, PNG this study aimed to:

1. Describe and understand the health service user journey experiences of people diagnosed with TB.

2. Identify the socio-ecological determinants of access and utilisation of TB services (screening, diagnosis, treatment and care).

3. Describe how household dynamics influence TB transmission risks.

4.2.2 Study design

This was an exploratory qualitative study of 20 people who were accessing TB treatment on Daru Island in South Fly District, PNG between January and February 2018. This was a research project, separate from routine programmatic activities and data was collected as part of a larger research project that also interviewed 20 household contacts of TB (not reported in this thesis). The study was guided by an interpretative approach that acknowledges the importance of accessing locally situated, subjective understandings of the socio-cultural context of TB care.[461] This study was conducted and reported according to the Consolidated Criteria for Reporting Qualitative Research (COREQ) guidelines (see Appendix 4.1 for the completed checklist).[462]

4.2.3 Reflexivity statement

The research was conducted collaboratively by a multidisciplinary team comprising four Papua New Guinean and four international researchers; PNG research partners and WPHA TB program leaders; supervision from expert social science, clinical and public health researchers; and community researchers (locally based in Daru). The study was endorsed and sponsored by the WPHA (Morris). I, as the principal researcher (an external non-PNG researcher with clinical and public health expertise in TB) designed the study and supervised data collection but did not conduct interviews directly. The research team comprised senior qualitative researchers who supported study design (Mason, PhD; Kelly-Hanku, PhD; Mek, MSc) and analysis (Bell, PhD), who also supported and trained Daru-based researchers (Burko, MPH; Dorogori; Arona) on methods for study implementation.

As an external researcher with involvement in TB program implementation, I recognised potential influences on the research process. To address this, local community researchers conducted all interviews to ensure cultural appropriateness, though their insider status also posed considerations regarding confidentiality in a small community setting. We recognise that our diverse lived experiences and multidisciplinary perspectives shaped our collaborative approach to the research.

4.2.4 Setting

The study was conducted on Daru Island, SFD, Western Province, PNG. The setting and model of care for TB have been described in more detail in Chapters 1 and 3. Decentralisation of TB services outside Daru remains limited, with only two other health facilities in South and Middle Fly offering TB diagnosis, Mabudawan and Balimo. Outside

of Daru, there is only a passive TB case detection model with people required to present to the closest health centre, then referred and travel to DPH for laboratory diagnosis of TB, clinical assessment and treatment initiation. This is a difficult and arduous journey for many, requiring land and water transportation and financial resources.

People from the mainland villages in Western Province will come to Daru and temporarily reside. Despite its small size and population, Daru has several informal settlements known as "corners" that correspond to respective villages from the SFD mainland, kinship groups and/or tribes. These corners serve as the primary accommodation option for both permanent and temporary migrants. This includes people seeking health services (including TB care), access to services (education, employment, commerce), economic livelihoods and/or family and social reasons.

4.2.5 Participant sampling and recruitment

Twenty study participants were sampled purposively to generate a broad understanding of TB care journeys. A form of non-probability sampling, purposive sampling occurs when researchers strategically select participants based on certain characteristics and experiences that are of relevance to the research question being investigated.[463]

To explore the study aims, individuals were eligible to participate in the study if they were on at least two weeks of TB treatment; currently resided on Daru; and were aged over 18 years. A purposive sample frame was used to explore diverse experiences, with the minimum targets displayed in Table 4.1. These were chosen to be either representative of the known cohort demographics–age, gender, residence outside Daru; or reflect priority characteristics (MDR-TB); or provide balanced insights across the care journey (stage of treatment, ward in Daru).

Data collection continued until the predetermined sample targets were met rather than until theoretical saturation was achieved, consistent with the study's exploratory aims and pragmatic constraints

Table 4.1 Sampling frame with targets for qualitative study of people with TB

Characteristic	Category	Minimum target (%)	Sample
Gender	Female	50%	10
Age	18-34 years	75%	15
	≥35 years	25%	5
TB Diagnosis	Drug-susceptible	40%	8
	MDR-TB[1]	60%	12
Stage of Treatment	Early (<2 months)	30%	6
	Late[2]	40%	8
Place of Residence	Outside Daru (original residence)	30%	6
	Ward in Daru	25% (equal distribution across 4)	5

[1]Multidrug- or rifampicin-resistant TB (at least 2 with extensively-drug resistant TB)

[2]>3months DS-TB, >6 months MDR/RR-TB

Potential participants were identified from treatment registers by the research team, in consultation with the clinical team. Potential participants were invited by frontline healthcare workers (treatment supporters, community nurses, peer counsellors). To reduce risks of coercion, no individual was directly approached by a member of the research team to participate in the study. Participants were not provided financial or material payment to participate but were provided with refreshments up to the value of 10 PNG kina (3 to 4 Australian dollars) during participation.

4.2.6 Data collection

A qualitative semi-structured interview guide comprising open-ended questions was used to explore participants' experiences with TB (see Appendix 4.2). Semi-structured interviewing using predetermined open-ended questions permits researchers to probe deeper into responses and adapt questioning based on participant responses.[464] This method is well-suited to sensitive health research, as interviews provide a conversational framework that enables generation of rapport and trust. Interviews allow participants to share experiences in their own words and prioritise issues most important to them. [464] These benefits were deemed suitable for this study to explore how participants' health service journeys intersect with socio-cultural influences in their lives and communities.

Interview guides (see Appendix 4.2) were developed with WPHA TB program leaders and PNG research partners to ensure that the guides were appropriate to local context. The interview guide was designed to learn more about the illness and treatment experience of people diagnosed with TB.

Two community researchers (one female, one male) who were from Daru, were specifically recruited and trained for this study. They conducted all interviews to ensure cultural appropriateness and language accessibility. Both research assistants were fluent in English, Tok Pisin and Kiwai, the predominant local languages, and had existing knowledge of the community context. As community members who did not have a role in TB program implementation, they were selected deliberately to reduce potential power imbalances and coercion between researchers and participants, facilitate trust-building, and ensure cultural sensitivity.[461] However, their local connections and relationships within communities posed potential challenges, including participants' concern about confidentiality within a small community, modified responses based on perceived social expectations, and bias in participant recruitment favouring family and friends.[461] To address these considerations, sampling and recruitment processes ensured that community researchers had no social or cultural connection to participants, and extensive training was provided on research ethics, confidentiality protocols, and interview techniques by two experienced qualitative researchers.

To support the two community researchers, an initial four-day training workshop was conducted in Daru, which covered TB epidemiology and care (including infection control), study protocol, principles of qualitative research, ethics and confidentiality, recruitment and consent, interview techniques and note taking. Thereafter, community researchers were supported by Mason and Burkot with on-the-job training, mentorship and supervision for the first five interviews each. To ensure quality of data collection, a study standard operating procedure was developed and monitored. Infection control training was provided, and respirators were provided for the field research staff.

Written informed consent was obtained from all participants, and a participant information sheet was provided prior to interviews (see Appendix 4.3). Interviews lasted between 14 and 92 minutes (median 54 minutes) and were conducted by two community researchers in English and Tok Pisin / Kiwai. Interviews were conducted in outdoor settings (for infection control) that were audio-private locations chosen by participants, including community clinics and hospital grounds. An interview data sheet recorded key demographic information and any notes from the interviewer. All interviews were audio-recorded, and data sheets scanned. Audio files and scanned documents were saved on to a password protected computer managed by the research team. Interview transcripts were not returned to participants for review.

4.2.7 Data analysis

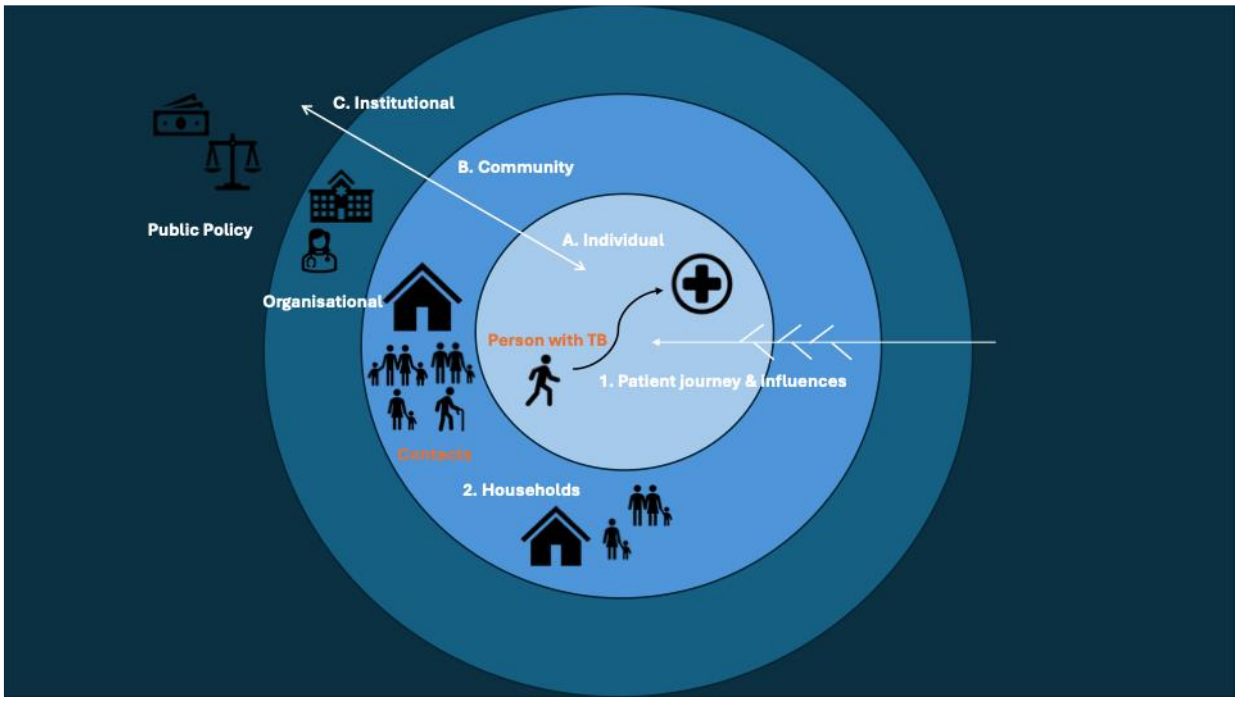
Interviews were transcribed verbatim and translated into English where necessary. The transcripts were imported into NVivo (version 15, QSR International Pty Led, 2023) in preparation for thematic analysis by the principal researcher, with guidance from a senior qualitative researcher.

Thematic analysis followed Braun and Clarke's six-phase approach[465]: (1) data familiarisation by reading through the transcripts and making notes; (2) generating initial codes; (3) searching for themes; (4) reviewing themes; (5) defining and naming themes; and (6) reporting the outputs. The analysis process used a hybrid of inductive and deductive approaches. Initially, inductive approaches were used, allowing initial codes and themes to emerge from participant narratives, while prioritising community perspectives and voice (phases 1-3). Deductive elements were then incorporated to further develop themes, by connecting findings to the research objectives and a socio-ecological framework (phases 4-5), adapted from McLeroy,[460] which organised themes according to levels of influence (individual, community, institutional). Analysis was conducted by the principal researcher (Majumdar) and then discussed with an experienced qualitative researcher (Bell) to ensure methodological rigour and challenge emerging interpretations.

To guide the thematic analysis and reporting of findings in this chapter, a conceptual framework was developed (Figure 4.1). The framework was structured around two central domains – (1) TB care journey and influences along the journey (objectives 1 and 2); (2) understanding households (objective 3) – and the adapted socio-ecological model to analyse contextual influences at (a) individual, (b) community (i.e. family, kinship and community) and (c) institutional (organisational, policies, societal) levels. From this, a detailed coding tree was developed and is presented in

Table 4.2 showing the themes and hierarchical coding structure. Results are presented according to this coding structure.

Figure 4.1 Conceptual framework using a socio-ecological model for thematic analysis



Domains (1 to 2) and Socio-ecological model (A to C)

Table 4.2 Coding structure for thematic analysis

Domain 1: TB care journey and care experiences of people with TB
1.1 Participants' TB care journey and experiences
1.1.1 Symptom recognition and diagnosis
1.1.2 Treatment initiation and adaptation
1.1.3 Ongoing TB care and management
1.2 Socio-ecological influences along TB care journeys
1.2.1 Individual level influences (A)
1.2.2 Family, kinship and community level influences (B)
• Local support systems
• Socio-economic barriers
• Community stigma
1.2.3 Institutional influences (C)
• Healthcare worker engagement
• Model of care challenges
• Limitations of centralised TB and healthcare
Domain 2: Understanding households
2.1 Household composition and overcrowding
2.2 Movement between households in SFD
2.3 Household TB risk

4.2.8 Ethics

Ethical approval was obtained from the PNG Institute of Medical Research IRB (1708), PNG MRAC (17.34) and Alfred Hospital Ethics Committee, Australia (507/17). The study was endorsed and approved by the WPHA program and was included in the TB implementation plan.

Written informed consent was obtained from all participants (see Appendix 4.3). No identifiable information was collected or shared. Interviews were conducted in mutually agreed safe environments where the participants feel safe both physically and emotionally, in an outdoor space. Only the participants and researchers were present (either one or two interviewers). Interviewers were briefed in counselling strategies to develop interviewer awareness surrounding cues and/or signals by which the participant was indicating distress. If the interviewers judged there to be negative emotional or psychological impact from participation in the interview, the interview was terminated and a referral to the counselling team was arranged for counselling and support. Confidentiality and anonymity were preserved through de-identification and use of a study ID on all written collected data. The only personal identifiers collected were on the consent form and audio transcript, which were stored securely. Audio transcripts were deleted after transcribing.

Participants received the standard of care available in Daru, to ensure the best available health outcome. Screening, diagnosis and treatment for TB was conducted according to the NTP guidelines and program standard operating procedures. Patients with non-TB health issues were referred and accompanied DPH for assessment and management.

4.3 Results

Forty-two potential participants who met the eligibility criteria were identified and approached by frontline staff, of whom 28 met with the research team. Twenty of these people with TB consented and completed an interview. Some participants initially consented but either didn't attend the appointment, withdrew consent or commenced the interview but then withdrew (two participants). Cited reasons for non-participation varied and included the lack of payment for participation, not feeling well enough, need to travel or social activities and spousal refusal of their participation. No repeat interviews were performed.

Results are presented according to the thematic framework outlined in

Table 4.2. Analysis of the 20 interviews revealed four critical issues that shaped participants' TB care experiences: innovations in person-centred care, socio-economic vulnerability, service access and centralisation, and household transmission dynamics.

4.3.1 Demographic and clinical characteristics

Clinical and demographic characteristics of participants are displayed in Table 4.3. Interviews were conducted with 10 females and 10 males with a median age of 37 years (range 18 to 72 years, interquartile range 28 to 49 years). All were receiving TB treatment in Daru– 13 for MDR-TB, 2 for extensively drug-resistant TB (XDR-TB) and 5 for DS-TB. Of these, 10 were on treatment with a regimen containing bedaquiline. The median treatment duration at interview was 8.4 months (range 1.2 to 19.6). Seventeen people had pulmonary TB and three extrapulmonary TB (including 1 person with both).

Eleven participants reported their status as married, 7 were single or not specified and 2 were separated. Only 2 participants had formal employment (1 teacher, 1 community health worker), 2 were retired and 16 were unemployed or had informal employment. Of these, 5 were market sellers (informal) and 2 relied on fishing. Eleven participants were from outside Daru, from villages in South and Middle Fly, travelling to Daru for TB care.

All participants, except 2, resided with extended family members (outside their direct family). This commonly included living with parents and siblings and sharing housing with multiple families. A more detailed description of each participant is displayed in Appendix 4.4.

Table 4.3 Demographic and clinical characteristics of TB cases interviewed in Daru, Papua New Guinea (n=20)

Characteristic	n	%
Gender		
Male	10	50
Female	10	50.
Age (years)		
Mean ± SD	38.5 ± 17.4	
Median (IQR)	36.5 (28-49)	
Range	18-72	
Age groups		
18-29 years	7	35
30-39 years	5	25
40-49 years	4	20
50-59 years	1	5
60+ years	3	15
TB Type		
Drug-sensitive (DS)	5	25
Multidrug-resistant (MDR)	13	65
Extensively drug-resistant (XDR)	2	10
Pulmonary	17	85
Extrapulmonary	3	15
Original residence		
Village/Rural	11	55
Daru	9	45
Relocated to Daru for TB care	6	30
Employment status		
Unemployed	10	50
Self-employed/ market sales	5	25
Employed (Health/Education)	3	15
Retired	2	10

4.3.2 Participants' TB care journey and experiences

Participants' care journeys through TB diagnosis and treatment on Daru Island were often complex experiences, marked by diagnostic delays, treatment initiation challenges, and ongoing difficulties accessing and navigating care.

Symptom recognition and diagnosis

Most participants experienced classic TB symptoms including cough, fever and weight loss. One man ***(TSN, male, 45, MDR-TB)*** said he had, "night sweats. I was coughing for some months", while a woman ***(SSW, female, 28, DS-TB)*** described *"coughing for 3 months"* and feeling short of breath, explaining*, "when I saw that it's 3 months, now I went down to health centre."* The duration between symptom onset and decision to seek care ranged from immediate in some, but most participants experienced long delays with prolonged symptoms before seeking care.

The decision to seek care often occurred when symptoms affected their ability to function, became disabling or family members raised concern:

> *"I had sleepless nights, sweats at night, I coughed for too long, I was losing weight, bit of headache, back pain. I just lazed around during the daytime, I was just sleeping only. I don't do work. So for almost two months, I was sleeping only. My mum decided to take me to the TB hospital. So when I went there, blood test and everything, the checkup, they said, 'Oh you are suspect with the MDR TB.' So they put me on treatment."* ***(NTT, male, 21, MDR-TB)***

> *"In the village, every time we are working. Like making garden or houses… I used to wake up early in the morning and go to the garden and come back in the afternoon. Then it started like, I woke up in the morning, wash and do little bit of work, and go back to sleep again. Then walk around and go back to sleep again. I was like that and the cough started. I didn't know myself that I was getting this type of sickness like TB… Until one day, I was coughing and I was vomiting blood. That same time I lost weight. Then I had to tell my relatives, 'can you take me to the hospital?' So it started first before I was put on TB medicine.* ***(JDA, male, 49, MDR-TB)***

The delay was more pronounced for participants with extra-pulmonary TB. One woman ***(IDS, female, 51, DS-TB)*** said doctors thought she was *"suffering of this chronic migraine headache.. for those three years.. when they didn't know that I (instead) had this brain TB".* She experienced a three-year journey of misdiagnosis, where her

symptoms of blindness and speech difficulties were initially treated as neurological problems until spinal fluid testing revealed TB meningitis. For others, a gradual onset or misattribution of symptoms led to treatment delay and self-medication attempts. For example, a woman ***(SUB, female, 28, DS-TB) described "***taking the normal antibiotics at home" for a couple of months before testing for TB:

> "*I was a heavy smoker and I'm a heavy chewer. I was thinking that the causes were from the drugs that I was taking… I went in to take some antibiotic treatments but then it did not help… Septrim, amoxicillin, Panadol, been on injections, been on the nebulizer. When it did not help, my only option was to get back and get my sputum. I straight suspected that I could be infected with TB.*"

Another woman ***(PBO, female, 31, MDR-TB)*** described symptoms of weakness and weight loss which led her to strongly believe she had TB. However, as she was not coughing or able to produce sputum, her diagnosis was delayed. She attempted self-remedies, and doctors tried other treatment over a 2-month period until she could be diagnosed:

> "*I tried to take other medicines… I tried to steam myself, and take some herbs… [after] about two months they started doing investigations and it took long time. Because I was not coughing, so they didn't detect anything. But my feeling was telling me that no, I was not right. And I keep persisting [telling] doctor I'm not right…They wanted me to produce a sputum and it took long time. It took about a month. I tried to do something to make myself cough for some time… I started taking other drugs. Like coming to the hospital, treating me with medicines, antibiotics, Panadol or whatever that I was taking, but it never helped me. For about two months..That's when I produced the sputum.*"

Symptoms had a significant impact on people's lives, resulting in inability to work (including caring) or carry out usual daily activities. A woman ***(STA, female, 30, MDR-TB)*** detailed that she was unable to continue subsistence fishing, explaining, "*when this sick got me, OK me and my husband stopped from the reef. Now I'm suffering.*" Another woman **(*SUB, female, 28, DS-TB*)** said**,** "*It affected me because I couldn't do the things as usual that I did… heavy laundries for my kids.. cook meals for the family*."

People's diagnostic experiences varied considerably. Some patients received rapid diagnoses while others faced extended delays. A patient with pulmonary DS-TB described a smooth, systematic journey:

"When I took my X-ray they told me that I had some inflates (infiltrates) in my left lung. After I realised that I had inflates in my left lung I straight away asked them that I wanted a sputum. I gave my sputum straight away and they found out that I was positive TB." ***(SUB, female, 28, DS-TB)***

However, diagnostic complexity emerged for patients without typical symptoms. Empirical treatment trials with antibiotics prior to TB diagnosis, or trial of DS-TB treatment prior to MDR-TB diagnosis, were common:

"In my case it took couple of months because I didn't produce sputum… they commenced me on DS TB first for two weeks… But then it didn't help me so I came back… I was helping myself to produce sputum. From there they diagnosed that I had TB…The sputum showed positive MDR." ***(PBO, female, 31, MDR-TB)***

"First I was on DS treatment and then it was still on positive (after 6 months)…then they find out that I had MDR. ***(MNB, female, 18, MDR-TB)***

Treatment initiation and adaptation

Treatment was initiated promptly once the diagnosis was made. Five participants were initially hospitalised, all with MDR/RR-TB, including two with extensively drug-resistant TB (XDR-TB). The remainder were commenced on treatment in the community.

Continuing the journey from ***(SUB, female, 28, DS-TB)*** above, she describes smooth experiences in being tested for HIV, having an X-ray, counselling (including a booklet) and treatment initiation: *"they explained that I will be put on DOTS [DS-TB treatment] and this medicine is powerful and it will cure my sickness if I am going to be faithful to the medicine. If I will miss my medicine, then it will become resistant to my body. So I took their advice, I sat down, got counselled, after counselling they straight away they put me on the treatment. That same day I got my treatment."*

Transition to MDR-TB treatment was more difficult than DS-TB, largely due to the side effects and pill burden of the medications. One participant with extensively drug-resistant TB described her overwhelming experiences while she was in the ward: *"They put them all, twenty of them. I was scared, I'm really scared to drink all this medicine. Twenty of them and sister told me, 'I'm going to stand here and you will drink all medicine, twenty medicines and finish them.' I started getting one, one. I get one medicine tablet in the mouth and I started vomiting and the sister will say 'no, don't do it, don't do it!' I continued like this until I finished the medicine. They told me, 'you lie down, we will give you injection*

same time.' The working ladies, same time they gave the injection. That amount, twenty medicine, I used to drink that amount over here in the hospital." ***(STA, female, 30, MDR-TB)***

Other participants reported positive experiences on treatment commencement, particularly after provision of information, education and/or counselling from health workers. One man ***(TSN, male, 45, MDR-TB)*** said***, "****I was really happy to get my medicine",* because after diagnosis *"I was thinking that I have to get the right medicine at the same time."* A woman ***(PBO, female, 31, MDR-TB)*** explained she knew she had TB because of the symptoms, and said, ***"****It didn't make me worried… I was having positive mind that I was having TB and I really wanted the doctors to put me on treatment."*

For some, positive treatment initiation experiences were backed up with dramatic and rapid improvements: "Straight after I was put on TB treatment, I saw the change within three weeks' time that I was so overjoyed after all. This headache just went out, left me and I was happy." **(IDS, female, 51, DS-TB)**

Ongoing TB care and management

While participants recognised the benefits and importance of TB treatment, their journey into TB management involved significant challenges. There was significant burden placed on participants through complex medication regimens requiring daily interaction with health care workers, significant side effects, logistical challenges related to attending daily clinics for medication, and socio-economic hardship associated with loss of ability to generate income or perform duties.

MDR-TB treatments administered during the study period (prior to the development of short, all oral regimens) had considerable toxicities. When one man ***(TSN, male, 45, MDR-TB)*** started taking treatment, he described his "*legs getting numb or getting cold, dizziness… fingers getting numb".* The side effects from the injectable drugs for MDR-TB were particularly significant. A woman ***(PBO, female, 31, MDR-TB)*** describes the devastating symptom of hearing loss after being on injections for about five months. She said, "*After five months I started feeling this knee pains first. Then after the knee pains, I started feeling this numbness. And then I developed hearing problem. I wasn't hearing properly."*

A young man described a similar experience; *"Hearing problem, small some of it just started coming up, and then now it's like a bell ringing in my ear, both sides. This side is*

like almost completely blocked, this side is like just a little bit okay. And then the joint pains." ***(NTT, male, 21, MDR-TB)***

During the study period, the TB program introduced a new, better-tolerated MDR-TB medication, oral bedaquiline, to replace the injectable medicine. Ten participants received bedaquiline and reported positive experiences: *"I go to bedaquiline after four months [of injection]. They completely stopped the injection… We were the first patients who started on this drug…Definitely, that was a very big change that I got from the injection on to the bedaquiline. As soon as I got on to the bedaquiline I quickly regained my strength. It took me about two weeks, I started working in my garden. I got the bushknife and spade. I cleaned around. Maybe I made around three plots at that time. It really helped me. Even I could carry the 10kg buai bag on my head."* ***(MBA, female, 47, MDR-TB)***

> *"Paining, trying to breathe is paining. That's from injection so they cut the injection and put me on bedaquiline. When I get bedaquiline, paining stop."* ***(STA, female, 30, MDR-TB)***

Throughout the study (and since 2016), treatment provision was community-based, at five treatment sites ("DART" sites) where meals were also provided. The NTP protocol requirement for DOT created significant logistical challenges and placed the responsibility on the patient. Patients still had to travel distances to fulfil daily treatment attendance, where TB patients were allocated a treatment supporter who provided supervision:

> *"There is a problem there at World Vision too. If a patient is not there, they don't go and look for that patient down at the corner, where is he? They will start getting cross, but that's your responsibility to go and look for the patient where he is…every day, daily you are getting medicine, so you must be on time to get your medicine."* **(*EWV, female, 36, XDR-TB)***

> *"I have only these supporters here. I come here, get medicine and then I go back. Sometimes I go direct, if I am not satisfied, I go direct and tell the doctor... Well, the best thing they do is at least they come here and they give us medicine, advice, ask us 'how are you feeling?'. And they are always open to us, at least encourage us to take medicine every day, don't miss, come, take medicine. That's what I can say."* **(*JAN, male, 43, MDR-TB)***

However, the TB program in SFD had been adopting a more person-centred approach with patients offered flexible arrangements including home visits and self-administered treatment ("supply"): *"I requested that they give me one week supply and I take my medicines at home... So only at the weekends I report back to the DART site and they give me the one week supply.. I treat myself at home with the trust. With them trusting me and me trusting myself to take my treatment honestly."* ***(SUB, female, 28, DS-TB)***

The introduction of regular peer education and counselling sessions (in 2016, by Burnet Institute) was a key person-centred care dimension to address medical and psychosocial needs: *"The counsellors, they just come like monthly for sessions, like just to check on us if we are doing fine, are we facing problems with our treatment or with the families or any other things. Just checking us if we are okay, encouraging us not to take other drugs, smoke or drink or do other things, advising us and giving us encouragement to take the treatment faithfully and eat plenty."* ***(NTT, male, 21, MDR-TB)***

4.3.3 Socio-ecological influences along TB care journeys

Analysis of patient interviews from Daru Island reveals diverse influences operating across all levels of the socio-ecological model, shaping treatment experiences and outcomes for TB patients along these care journeys.

Individual level influences

Individual level influences related to knowledge and personal experience with TB. Overall, participant knowledge about TB was good, supported through personal and family experience, and was not a major barrier to care engagement. Participants interviewed had a strong desire to be healthy and accepted new information from health workers, including those with limited pre-existing knowledge.

Knowledge of TB in the family led to earlier recognition and care seeking for TB diagnosis. A woman, (***EWV, female, 36, XDR-TB)*** knew about TB because *"my big brother, he got that sick [i.e. TB] and he died. And the other one too… and my child... From them I experience about how TB is."* She explained she was able to recognise her own symptoms as needing hospital attention: "*because I got the experience, I was looking after my big brother who used to tell me and doctors, I used to hear from that, when you feel like that you must always come to the hospital because this sickness is in the family. So I told small sister, you have to take me to the hospital, I'm not feeling well. When I cough, I feel like my ribs are paining, and hotness. And I feel dizziness in my head…. because the sickness was in the family, so straight away I knew that I'm having*

that. Because of my experience, that's why I told small sister 'you take me up.' So I came up to the doctor and they found out that it was TB."

When asked what they knew about TB prior to diagnosis, participants said, "*Coughing. It's airborne disease. When you talk with somebody, that's the time it will pass"* **(*MNB, female, 18, MDR-TB*)**, and *"it's airborne, only cough will pass it"* **(*STA, female, 30, MDR-TB*).** It was notable that participants with limited educational opportunities and experiencing socio-economic disadvantage referred to TB as airborne and had knowledge of the route of transmission and cough as the main mechanism. On the other hand, there was a common misconception around the transmission (or prevention) of TB through sharing food and utensils among several participants. There was very limited use of traditional medicine among participants. Only three participants made references to sorcery or magic – it was not a dominant factor in knowledge or experience.

These understandings were consistent with extensive community engagement and health promotion messaging conducted in Daru in the years prior to the study. Participants noted the importance of TB awareness and education. For example, a woman ***(SUB, female, 28, DS-TB*** explained that there was awareness raising in schools for teachers and students, as well as a *"team that came around to different residential areas… doing awareness on the TB itself and how it infects people."* Another woman ***(IDS, female, 51, DS-TB)*** said that she *"heard from volunteers who are employed by TB. I got information from them, how they used to introduce the symptoms."* Two others noted the vital role of the peer TB counsellors in providing trusted health information:

> *"I knew that there was TB around in Daru Island, but I was not taking it so serious… I was not really well informed. But I knew that it could be passed, it's an airborne disease. I only knew that. But later when I was already on the process of sickness, when the counsellors came, that's where I was well educated about TB.* ***(MBA, female, 47, MDR-TB)***

> *"No, no, when the sick got me that's where I came to know. Counsellor was talking about TB, that's where I knew about TB."* ***(DAN, male, 20, MDR-TB)***

Family, kinship and community level influences

Local support systems

The traditional PNG kinship system resulted in complex dynamics of obligation and assistance that could either facilitate or undermine the treatment journey. However, often, family support systems fundamentally shaped patients' treatment experiences, offering treatment support through both material and psycho-emotional pathways. A woman ***(EWV, female, 36, XDR-TB)*** said that her family reacted positively, stating; ***"****they helped me, they advised me because my father is a teacher also and he always encourages us... All of them supported me in the hospital."*

An elderly man described how his children helped him: *"A number of my children are working and they are supporting me. And I also do street sales just to keep me going, you know, making me busy near the house rather than sitting down and become useless." (****ADT, male, 72, DS-TB)***

People depended on these family and kinship networks for their livelihoods and there was a deep economic interdependence and social obligation. Women were in central caregiving roles, in addition to any formal or informal employment: *"My small sister also is working. There are only three of us, two girls and she is working so I used to help her. And when she get her pay she always help me to make small business. That's how we are living…Like I'm the mother… I was thinking about the family, because I'm the one working. I do work in the house and look after the family."* ***(EWV, female, 36, XDR-TB)***

As PNG is a very strong faith-based society, religion provided important emotional support to participants: *"My Christians were encouraging me. Like, 'don't worry, don't look down to problems' or 'situations, sickness comes to help you' and also 'don't believe your faith in this sickness, you put your faith that God is going to heal you.'"* ***(HKS, female, 37, DS-TB)***

Socio-economic barriers

Food insecurity emerged as a critical but largely unaddressed social determinant of TB care. This was despite daily meals provided to all TB patients at DART sites - " *we have food problem here…" **(JDA, male, 49, MDR-TB)***

> *"Like sometimes there's nothing in the house, stay like that without food, or sometimes we don't eat or go to sleep without eating. Like I'm staying with my father and my father got knee problem and that's why sometimes find it hard to find food. And moving around without eating, my body just went small and I*

started coughing and this sick got me and sometimes I don't eat." ***(DAN, male, 20, MDR-TB)***

Financial hardship within families was a common experience and created substantial barriers to the care journey. Informal workers (market sellers, fishers) were most profoundly affected by TB-disrupted livelihoods due to absence of social protection, and the inability to earn money while sick.

> *"Sometimes when I was by myself, I left my family. I don't eat in the morning and I come and get my medicine, only I take lunch. Afternoon, I don't get something or get little from my relatives... Like, I get medicine but where will I go to get help to support myself and my family?…So as a patient, I'm still on the treatment and how can I go and find? According to my treatment, I cannot just move around and go fishing and get fish to sell. It's bit hard for me. I can go fishing but according to my treatment I cannot move myself because it's everyday treatment. And it's bit hard for us to get the supply to move around...the person I am staying with, is working in World Vision. Sometimes when he gets his pay, he helps us with K10 or K20 to get something for us. But beyond that, nothing."* ***(JDA, male, 49, MDR-TB)***

As this male participant described. Individual barriers need to be seen in the context of kinship-based economic interdependence. That is, in engaging in family support systems, looking after someone with TB within the wider family networks puts further strain on family support systems that are already pushed to the limits, as ***(IDS, female, 51, DS-TB)*** described: *"I had support from my relatives but seems like life is very hard, so just a little will do but still I lived on it."*

This participant gave a harrowing account of compounding socio-economic pressures and lack of support: *"At this very moment, like, my parents are in Moresby and me, I have a situation right now and nobody is really supporting me. Though my brother is working, like my real brother, the blood brother, the other one is in the village but the other one is here in Daru but he's not looking after me. I went through sort of situation, hard times here right now…Like, sometimes I don't eat because of I don't have any support. At this very moment, when I got this sick, like my blood brother, he really don't want to look after me... like he's to love me but as soon as he's under liquor, that's how like he will hate me. Something like chase me out of the house, when he's under liquor… So even though my husband – but like I went through a broken marriage, so right now I'm having a problem. So sometimes I don't eat. I go to sleep without eating, I will come*

get medicine, I will go. But I will pray to God that God will help me at this very moment." ***(HKS, female, 37, DS-TB)***

Community stigma

Community responses to TB were shaped by varying levels of knowledge and cultural understanding, sometimes creating environments of discrimination. Many participants did not, or were initially slow to, disclose their TB diagnosis to their family, due to fear and stigma. As one woman ***(IDS, female, 51, DS-TB)*** explained, *"I am ashamed because they, you know, might talk about me or make fun of me of this sick because everybody fear this sick."*

A few participants reported overt stigma and discrimination from their family members: *"It's like, when I don't do work around the house, or I'm walking around, or my body is tired, I don't get fed. Sometimes they hate me because I have this sickness. They tell me not to mix around with them or the kids. I must avoid them. So what I did, I just had to move across to live with (my uncle)"* ***(CBO, female, 23, MDR-TB)***

Self-stigma was noted as an initial barrier in the journey, with many participants initially concealing their diagnosis. This same woman ***(CBO, female, 23, MDR-TB)*** noted, "*When I was told I had MDR, I felt ashamed. I stop moving around in town. But as time went by as I took my treatment and the medicine worked in my body, I started to move around in public*." Her experiences of self-stigma changed with improved symptoms and education, counselling and understanding.

Institutional influences

Healthcare worker engagement

Participants described varied experiences with different categories of health workers, including treatment supporters, counsellors, community health workers (CHWs), nursing officers (NOs), health extension officers (HEOs), and medical staff. Many participants expressed positive feelings about their interactions with health workers, particularly appreciating the interpersonal aspects of care.

Medical staff were well regarded and trusted. However, treatment supporters received mixed and mostly negative evaluations, with approximately 8-10 participants expressing dissatisfaction compared to 4-5 expressing satisfaction. This man ***(NTT, male, 21, MDR-TB)*** had a positive experience, grounded in religious connection. He said, *"When every day we come for treatment they approach us in a good manner, say good morning. When*

we take the treatment we pray first over the medicines and everything, pray and then we start off our daily treatment. Their approach is good to us patients."

Counsellors provided foundational TB education and extended this to crucial social and emotional support, particularly in managing complex personal situations. They were a vital part of the model of care, providing psychosocial support to navigate treatment challenges and were trusted and valued by participants. One man ***(NTT, male, 21, MDR-TB),*** suggested the need for more counselling, *"Yes, it was really helpful... instead of the counsellors coming every month, they should be coming day to day.."*

A powerful example involved a counsellor who intervened in a patient's domestic conflict. In this example, the husband was not supporting his wife (the patient) with food: *"(the counsellor) got up and stop my husband, called my husband's name, '(F), come and sit down here.' He said to him, 'she is drinking medicine.. you must buy her food to eat. Don't just get cross to her.'"* ***(STA, female, 30, MDR-TB)***

Many participants expressed dissatisfaction with treatment supporters' approach and behaviours. One man avoided a DART site entirely due to treatment supporter attitudes; *"Like, some other DART site have problems, like problems with patients, with our treatment supporters have problems. I'm staying close to Tamati but because of that, we have attitude problems taking place in that DART site. That's why I don't get medicine from Tamati DART Site."* ***(JDA, male, 49, MDR-TB)***

Another participant ***(EWV, female, 36, XDR-TB)*** described harsh treatment and punitive attitudes**:** *"They used to scream at us, don't come late, come early... OK they say like this, 'who is going to come late, she got no lunch'... We are patients, we got right to talk to you people."* This woman explains her frustration that treatment supporters did not empathise with patients, or seek to understand why they sometimes could not attend the DART sites. This would result in not receiving their voucher or food. Patients correcting medication errors was a recurring issue: *"they don't get (understand) our reasons, like sometimes (when we are) not feeling well... You know, patients got their right. They start discriminate. You don't get your medicine… they don't give them voucher... Sometimes we correct the World Vision people…when I see that this medicine is extra one they are putting (an incorrect dose)."*

Model of care challenges

The person-centredness of TB care was characterised by both strengths and significant limitations in accommodating individual patients' needs and circumstances. While

participants widely acknowledged the effectiveness of medical treatment, approximately 6-7 participants expressed dissatisfaction with the rigid, paternalistic nature of the DOT model of care, compared to 4-5 who expressed satisfaction with the approach.

One man (***TET, male, 61, MDR-TB***) conveyed frustration about DOT approach. He said, "*I see it as a depriving of rights for the patients…I walk here, I shouldn't be waiting to get medicine... And then coming back or waiting here for lunch, we should be resting."* Another participant described being subjected to inappropriate physical coercion by treatment supporters**:** *"We went to give the sputum cup, they used to force me. 'Hey you people cough, cough'. We cannot cough, we are drinking medicine and the medicine is stopping all the sick. We cannot cough... The treatment supporters there, they used to tap us. I told them 'please, one of us patients will vomit blood. Because you people are forcing us to cough.'"* (***STA, female, 30, MDR-TB***).

However, some participants were able to negotiate a more autonomous option for self-administered treatment, like one woman who had a kinship connection to a health worker: *"Yeah. My aunty that adopted me, her son is working there (at hospital). When I don't go and get my treatment he used to bring it down, when I was taking home DOTS. They used to bring my medicine down that way to the house. Yeah, they used to treat me there when I was expecting and doctors told them to make home DOTS for me."* (***MNB, female, 18, MDR-TB***)

One participant accepted the DOT model and the concept of being "faithful" to your medication, but was concerned about the risks of attending a clinic where people attended with other health issues: *"What I like about it is, like, going to take your medicine daily is best so that the treatment workers there may see how faithful you are taking your medicine. The faithfulness, there must be honesty of taking your medicine daily… I dislike taking my treatment in there because there are other patients with different type of sickness also at the same DART site. They can also be infectious to the normal TB DS ones that are there."* ***(SUB, female, 28, DS-TB)***

Related to this, community-based (DART) sites and patient support provided there (meals and vouchers) received mixed reviews. While appreciated for convenience and reduced travel requirements, significant concerns were raised about waiting times, voucher provision (being late) and privacy:

> *"The only thing I dislike was, it was public area. So our privacy was public. So yes, we have people walking on the road and then they see us and we are there. So sometimes I feel like my privacy is not hidden."* ***(MBA, female, 47, MDR-TB)****:*

> *"You cannot force us to come and wait for lunch here. I see that is not good. That should be changed, I cannot recommend on that. I cannot come back from there and drink medicine and then go back and then come back. Waiting, I cannot wait here, I need to rest and sleep. I cannot wait for food. Yeah, so they need to improve in that.* ***(JAN, male, 43, MDR-TB)***

Several participants raised concerns about the voucher system, which highlights the issues with material and financial enablers in an economically deprived community:

> *"They really need to improve on voucher… People used to come and argue about voucher here… You don't understand how we go through when we are on medication…I see that they really need to change their way or approach of giving voucher. According to the patients' rights, our rights have been deprived. You cannot give an overdue voucher…You cannot give voucher from some three or two months, that's overdue...They need to change, really change, do away with that process.* ***(JAN, male, 43, MDR-TB)***

Despite the food insecurity in Daru, multiple participants criticised the nutritional quality and lack of variety of the meal program delivered at DART sites. The standardised approach did not meet community or cultural needs:

> *"Those food they used to give us, sometimes we patients don't feel good eating. Every day that chicken rice. Every day chicken rice. Sometimes I don't eat those things... Sometimes you know patients, they drink this medicine, they feel like vomiting and they don't feel good."* ***(EWV, female, 36, XDR-TB)***

Limitations of centralised TB and healthcare

Geographic and access barriers in Western Province created fundamental challenges and inequities in TB care for participants from mainland villages who were required to travel to Daru for diagnosis and care. The large distances and long journeys were compounded by delays, with participants often visiting the health centre multiple times over several months before receiving a diagnosis of TB. When this was made, it was up to them to find the financial means to travel to Daru. The first step in the remote patient's journey was travelling to the aid post from their village. An aid post has only basic medications, like antibiotics. The next level of referral is a health centre, which is a primary care clinic. Most are not functional and do not have TB services in SFD.

This man ***(EMA, male, 38, XDR-TB)*** from Madiri village in Middle Fly District describes his journey and the major barriers to timely care. It was an approximate two hour boat

journey from his village to the health centre (Tapila), and then over eight hours via boat to Daru.

> *"I knew about TB so when the sick started on my body, I felt that I was only sick but as I have told you people, the transport-wise you must have money to buy fuel. You must have money to pay the transport to bring you this way. Did I mention that? Because those are the main basic things people need in the villages in the remote areas. So that was the thing. So I spent about two months in the village and then the third month I was there at the Tapila health centre and the HEO have to write a referral letter for me and he have to make radio calls this way, radio calls. It took about a month, yeah. And then the dinghy here went from here to the village, up to Suki, and then picked up me on the way, picked all the patients, and then came back this way."*

The enormous geographical, logistic and physical challenges were described by the same man from remote Kondobol in East Trans Fly (40km from Tapila health centre), who highlights what is required in terms of support, as well as the significant health risks of these long journeys:

> *It's a day walking. Sometimes when the patient is taken, when they walk through the bush track takes them two days from the aid post to the health centre. But you know we have two ways provided. We use our own dinghies, but if there is no fuel then we will have to paddle. We paddle on the canoe for two days and then come to health centre. And then from the health centre, you know, the staffs down there decide which patient to go….It's almost 40 litres of fuel. But traveling in the bush track, it's a hard job, it's a hard thing that I cannot express. You know what I normally express is a bush ambulance, 4 men have to carry the patient down when he's very weak... So what people normally do, they carry patients, but sometimes they die on the way. But I want to tell you something very important here. There were about 4 patients that have died from my area and then 3 from my own village. They came here, they were treated, and then they were sent home with the drugs. And then one time when we were traveling on the way one of then died at Tapila because the weather was not good, the sea was rough, the patient was cold, very cold…Another one was last year, the patient was treated, she was on TB treatment, she was a cousin to me. When she was sleeping she died on the way…You know I have a big concern for my area, especially my people, and I have been barking all around the place,*

understanding that I want the services to reach out. This program can extend. " ***(TET, male, 61, MDR-TB)***

Accommodation challenges emerged as one of the most important barriers affecting the TB journey, particularly for patients who relocated to Daru from mainland villages. The inadequacy of accommodation options created cascading effects on treatment adherence, family relationships, and overall wellbeing. Participants arriving in Daru for TB diagnosis or treatment faced immediate housing crises. The man from Kondobol ***(TET, male, 61, MDR-TB)*** eventually arrived in Daru but was not able to find accommodation and faced community stigma;

> *"When I first came in I slept under the house where the rain came and then in the night there was a big rain, the floods just went under the house, I had no place to go... Because most of these TB patients, they ignore them. You know sometimes they put the canvas and they sleep, no matter how the situation is bad, but they have to stay on the treatment because they are concerned about their life."*

The migration of people to Daru due to the lack of decentralisation of TB and health services exacerbates pressures on already strained housing resources. People's search for accommodation becomes an additional burden during an already challenging treatment initiation period. As one man ***(EMA, male, 38, XDR-TB)*** explained, *"When we come here we don't have proper accommodation where we can go and stay. And then when you want to use somebody's house, you have to negotiate. You will have to discuss it."* He also faced difficulties in remaining connected to his family in the village due to the limited telecommunication infrastructure. When asked if he has contact with his family, he replied:

> *"No, not really. Just once, between Christmas and New Year's. I have to get the flex [mobile credit] from here and then I text the other person to tell my wife to come this time, she must use your phone and then I will talk with her… I talk to them about sending my food, and then how was your Christmas and your New Year's. The children were all okay, but I wasn't okay because I wanted to enjoy my Christmas and New Year with the children. So I just told her if any transport is coming down you just pass me my food, like banana and potatoes."*

The economic vulnerability was particularly acute for patients from remote areas who needed to relocate for treatment. The man from remote Kondobol in East Trans Fly said that he spends "*almost 2000, 3000 kina"* from his own pocket to access services. In his

interview he fiercely advocated for service expansion, citing the life-and-death consequences of centralized TB treatment access:

> *"Western Province is not Daru Island only. I saw it all the times in the newspaper and I said no, the treatment is only in Daru Island, not everybody else. Like I said, many people are dying out there. When the patient is on difficult situation, what we have to do is we hire dinghy for 5,000 kina just for one patient to bring him or her here so the relatives will have to afford that, but if the services are there they can be taken close by."* ***(TET, male, 61, MDR-TB)***

4.3.4 Understanding households

Understanding the household system in Daru can help understand people's TB care journeys due to the reliance family and kinship networks for support, the issues of transmission risk within overcrowded accommodation issues, and the potential of the household as a unit of intervention for service delivery. Households and family networks on Daru Island must be understood within the broader context of ongoing cyclical urban migration and healthcare seeking from mainland villages that has resulted in the "corners." Importantly, the centralised TB systems in Daru contribute to the movement of people into Daru and overcrowding of households. These circumstances create dense living environments in Daru conducive to TB transmission and migration patterns that may facilitate broader spread of TB.

Household composition and overcrowding

The household structures in Daru reflected complex, fluid arrangements that extended far beyond nuclear family units. Multi-generational and extended family households were common. A man ***(DAN, male, 20, MDR-TB)*** explained that there were 13 people in his home, where *"we built one small house and some are sleeping underneath and some are sleeping on top... 4 big adults and 9 small children." A woman* ***(STA, female, 30, MDR-TB)*** *said there were three families in her home, including, "another brother with four children and another brother with three children and me with four children."*

The composition of these households reflected the complexity in kinship and family relationships that included adopted children, extended relatives and individuals connected through marriage relationships:

> *"I don't have adopted children but two of my elder daughters have been adopted from me, so I live with my thirdborn daughter and fourth born daughter… I am staying with my brother and his children, at Katatai Corner. The house belongs*

to my brother... He's got six children but we stay with four children and two others are adopted by his wife's relatives" ***(IDS, female, 51, DS-TB)***

"(I live at) lasa corner with my relatives. I came from the village. I'm staying with [HK], he's working at World Vision. He got only one male, got married already. Two is me, and three is [HK] and his family. His son that is married is also living there but he got no children." ***(JDA, male, 49, MDR-TB)***

Movement between households in SFD

Participants' experiences showed that individuals in Daru maintain connections with multiple household units simultaneously, due to family and kinship relationships and work or care obligations. These relationships created fluid boundaries between households but also meant that TB exposure could occur across multiple household environments rather than being contained within single family units: *"(I live in) Frog Town. With aunty and uncle and with my parents, my real parents… I used to have problem with my parents. Not with my father but with my mother. That's why sometimes I don't sleep there at Frog Town. I used to go up to my big sister where she stays with the husband (Samari Corner). So that's why, I don't really come and get my medicine."* ***(MNB, female, 18, MDR-TB)***

In addition, people moved from mainland villages to Daru for TB care. A man with MDR-TB **(EMA, male, 38, XDR-TB)** relocated from Middle Fly to stay in the corners with relatives. He said, *"I come from Fly River. This is the second year of my medication… I am staying with my wife's relatives.... There are a number of us, a number of people living in the house."*

Similarly, another woman, ***(SSW, female, 28, DS-TB),*** describes moving to Daru from Mabudawan village for TB treatment. She said, "*I'm staying in the village so when I came for treatment here, when they put me on treatment here it was about three months."* She then returned to the village but returned to Daru due as the health centre was closed (the village health workers were in Daru for 2 months) and her two children were on TPT: *"So my this one [4 year old] and baby one, they are on IPT treatment so their medicines were trying to finish and this one was left with one packet only. So I was finding it hard. Transport are there but no fuel and without fuel you pay with money to travel. So this health dinghy went from here to pick up, I came down and I told the skipper that, oh like that our health workers are at Daru now, these two months now, I need to go with my two babies to Daru because both of them are on IPT treatment."*

Household TB risk

The structural factors of household crowding and extended multi-generational kinship networks with movement across households and to/from villages are key determinants of the high TB transmission risk in Daru. Limited space meant that household members often continued sharing sleeping areas, despite awareness of airborne TB transmission.

Many participants described TB transmission across multiple generations in their household or family. The experience of death from TB in the family was not uncommon as one woman (***EWV, female, 36, XDR-TB)*** detailed: "*My big brother, he got that sick and he died. And the other one too, that why I knew from there and my child also... From them I experience about how TB is."*

Another woman **(*SSW, female, 28, DS-TB)*** described multiple family members with TB, separated by many years, suggesting that there were multiple transmission events (due to the high levels of TB) and potentially structural risk factors for this family: *"I was still schooling, our small sister she got this sick TB. She was baby, we adopted her and her mother couldn't feed her properly... So from there I got married and my husband, he was on the treatment too. Year before last year. So I understand that from him I got this sick. He was on normal TB treatment…And also my father too, my father he was on treatment and then he finished his treatment."*

Only two participants described the ability to take adequate measures to separate themselves from family members to protect them against infection. Both were women, one working as a teacher and the other a health worker, so from higher socio-economic and educational background. One woman **(*PBO, female, 31, MDR-TB*)** described how she kept isolated from her elderly parents and husband when she was unwell and understood that treatment reduces transmission risk. She said, *"I told them that when I'm on treatment, then you people can come close to me. …I told my husband, you go to the village when I am on treatment after treatment you can come back.*" The teacher had knowledge of TB transmission from awareness conducted at schools and took measures to reduce risk for her family, while her three-year-old child was initiated on isoniazid preventative treatment (IPT): *"Normally with my three-year-old who was always near me, I had to send him away that same night. Even it was painful for him to sleep with the grandma. I had to ask all of them to sleep in their own beds and their own nets because I was coughing and I didn't want to infect my children."*

The mother above, ***(SSW, female, 28, DS-TB)*** described her experience with IPT: *"In the clinic they told me that it's a program now. When they find that father is with TB or*

mother is with TB, straight away they put the children on the treatment, IPT … Because of that sickness might spread on the family, so they put them on the treatment. And sleeping TB is something like…. Like you are healthy, and that sickness is now sleeping inside of you.. people are not seeing the signs on your body… I was thinking that it's for their good, it's for their next generation. Because they are the generation for next time and I was thinking of their good… I must stop this sickness early in my family, not to spread…." ***(SSW, female, 28, DS-TB***

4.4 Discussion

This qualitative study documents the health seeking journeys, service use experiences, and household dynamics of twenty people diagnosed with TB in Daru, Papua New Guinea. The analytical approach allowed understanding of the socio-ecological influences on TB care, access and transmission risk. Through comprehensive analysis of the TB care journey from symptom recognition through to treatment, we identified a complex interplay of barriers and enablers operating across individual, community and institutional levels that influenced people's experiences and TB risk. Four critical issues emerged – innovations in person-centred care, socio-economic vulnerability, service access and centralisation and household transmission dynamics. People's experiences with TB, along with the influences of the care journey are deeply embedded in socio-cultural contexts of SFD. Like in many cultures, and in particular Melanesia, family and kinship connections are the priority, providing support to sick individuals when the health system is unable to but also resulting in community-level barriers where obligations for care and interdependencies have precedence over an individual's circumstances.

While multiple global qualitative studies have documented the challenges of MDR-TB care,[466–469] this study represents the first qualitative exploration of TB care experiences conducted in PNG—though subsequent larger qualitative studies were later conducted in Daru by members of this research team.[152–155] The unique socio-cultural context of Daru—including informal 'corners' settlements, cyclical migration patterns, and limited health infrastructure —means that detailed comparisons with urban or different cultural contexts are not readily applicable.

4.4.1 Person-centred care innovations

The patient journey revealed significant variability in diagnostic timelines, treatment complexity, and support needs. This was highlighted through both innovations and limitations in person-centred care approaches that address both medical and social determinants of treatment success. Person-centred care is a pillar of the WHO's End

TB strategy refers to a model of care that is holistic, individualised, respectful and empowering and considers the person as central to the process encouraging informed, shared decision-making and self-determination.[470]

At the time of this study, the TB program had transitioned from the emergency response phase (2014-16) to the systems strengthening phase (2017-19) where person-centred care was a focus of the model of care (Chapter 3).[404,471] Elements included community-based (vs hospital-based) TB care at DART sites, flexible treatment delivery that moved away from DOT, meals and food vouchers for TB patients that provided material and nutritional support, and peer counselling that provided psycho-emotional support.[150] A TB patient representative group was formed and provided input and feedback and community engagement activities expanded to work with local leaders as case finding activities were conducted in households and for the systematic screening initiative.[151,397]

Participants expressed clear appreciation for the benefits of medical treatment while identifying concerns about rigid, standardised approaches that failed to accommodate individual circumstances at the community DART sites. The introduction of bedaquiline represented a particularly valued innovation, with participants reporting dramatic improvements in tolerability compared to injectable regimens. Participants showed sophisticated understanding of their treatment needs and some undertook active advocacy for modifications such as self-administered and home-based care. Medication supply arrangements allowing weekly medication collection demonstrated system flexibility while maintaining program effectiveness.

At a health service level, the quality of patient-provider relationships varied considerably. While treatment supporters received mixed evaluations due to inconsistent attitudes and medication errors, the counselling model emerged as particularly effective, providing psychosocial support that extended beyond health education to include advocacy in complex personal situations. This was likely due to the responsiveness of the peer counselling model to individual needs and has been a success in HIV care, particularly among vulnerable populations.[472,473]

The interview guide asked about spirituality and traditional healing, but these were not prominent themes. This likely reflects the dominance of biomedical care when accessible services are available, representing an important finding about health-seeking behaviour in this context.

In PNG, DOT has long been established as the standard of care, with both health workers and the community understanding that hospitalisation, followed by observed treatment

is required to treat TB. The associations of DOT with the concepts of “faithfulness to treatment” and “being a good patient” puts responsibility on the patient, rather than the system to provide care and address barriers. While WHO has shifted strategy to person-centred approaches, DOT brings with it a rigid and paternalistic model that contrasts with all other disease control programs.

The program in Daru was the first to innovate flexible, community-based approaches to TB care in PNG. Since, other programs in PNG have followed and demonstrated success in self-administered and family support models.[474] These experiences demonstrate that standardised approaches may conflict with diverse patient circumstances, person-centred care requires not just policy commitment but systematic implementation, with community involvement to address structural barriers to care delivery. However, even these innovative person-centred approaches operated within broader structural constraints such as socio-economic barriers and access, that limited their effectiveness.

4.4.2 Socio-economic vulnerability

Socio-economic circumstances created substantial barriers across the TB care continuum. Consistent with findings among vulnerable populations globally, economic instability and housing insecurity emerged as fundamental barriers to TB care engagement.[255] However, the intersection of traditional kinship obligations and the unique population migration patterns within Daru and to mainland villages created unique barriers not well-documented in existing TB literature.

The individual level was not a major influence on the TB journey. In fact, people’s knowledge of TB was reasonable, and often grounded in family and kinship experience. Community-level factors included the breakdown of traditional wantok support systems under the extended burden of TB care, creating complex dependencies that sometimes undermine engagement with services. This was likely the combination of the community stigma experienced by people with TB and unbalanced mutual obligations. Separation from socio-economic supports in villages created hardships for participants who had to migrate to Daru. People with informal employment (market selling, fishing) had no safety net during illness and described the most severe disadvantage, including lack of food, money and safety. There was a paradox that despite significant food insecurity in Daru, participants reported lack of satisfaction with meals, and experienced hunger. At the institutional level, the lack of comprehensive health insurance and social welfare policies left TB patients economically vulnerable, despite the provision of incentives such as food and vouchers.

The WHO End TB Strategy prioritises the need to reduce inequalities in TB care through provision of poverty alleviation and social protection.[20] One of the three impact indicators is the number of households affected by catastrophic TB costs, which are defined as when a patient spends 20% or more of their annual household income on TB diagnosis and care.[21] The determinants of these costs are loss of income, travel and in some countries, costs of health services.[475] A national survey conducted in PNG of 1,000 TB patients in 2018-19 (32.5% from the Southern region that includes Western Province demonstrated that catastrophic costs were experienced by 33.9 (95%CI31.0-36.9) of households with greater risks in people with MDR-TB.[476] In this study the mean monthly household income was USD346, equivalent to 1,132 PNG kina.

Policy solutions are required to address these determinants, including comprehensive social protection, TB-specific support packages (accommodation, food, transport) and integration with existing systems (e.g. nutrition programs and private sector networks). There is growing evidence that socio-economic support can significantly improve TB outcomes. A household RCT in Peru demonstrated that conditional cash transfers improved uptake of preventive treatment and treatment success.[98] In this program of research, it was important to note that social support was valued more highly than economic support.[70] Similarly, in Brazil, a national conditional cash transfer program was associated with substantial reductions in TB incidence and mortality, particularly among Indigenous populations and those in extreme poverty.[477] Application of cash transfer support to an already vulnerable community, with traditional systems of mutual obligation, needs careful consideration. However, in Western Province and Daru, there is a precedent with compensation payments from the Ok Tedi mine, which suggests potential acceptability of future TB-specific social protection interventions.[137]

Nutritional support represents another important dimension of person-centred care and socio-economic support. A systematic review of 8 studies found that nutritional interventions - including food baskets, macronutrient supplements, and micronutrient support - had potential for improving treatment adherence.[478] This review didn't include the largest RCT, the RATIONS trial in India involving 10,345 household contacts, demonstrated that nutritional support was associated with substantial reductions (38%) in TB incidence.[390] Nutritional support to TB patients was associated with improved functional performance status and a decreased risk of TB mortality. The daily meal provision at DART sites in Daru aligns with this evidence, though participant experiences highlighted the need for more comprehensive approaches addressing household-level food security rather than individual nutritional support alone.

4.4.3 TB service access and centralisation

A major factor that compounded this vulnerability to TB was the centralisation of TB services in Daru, requiring patients from mainland villages to travel for days (up to 400km) for diagnosis and treatment. This creates profound health inequities with life-threatening consequences. The remote geography of Western Province created life-threatening delays, with participants reporting deaths during transport and extended diagnostic journeys that impact outcomes and facilitate TB transmission. Poor geographical access to TB services has been shown in multiple settings to be associated with diagnostic delay and worse treatment outcomes.[479,480] A study from East New Britain province in PNG showed that decentralisation of TB services increased case detection, compared with centralisation.[481] A systematic review of decentralised care of MDR-TB showed that treatment success was more likely, compared with centralised care.[482]

At an individual level, the requirement to travel to Daru for diagnosis and treatment created cascading economic and social disruptions. Impossible choices were faced to access TB care - patient transport costs were extremely high (2,000-3,000 PNG kina), families had to separate (including parents from children), and support networks were left behind. At the community level, while the traditional kinship system meant that in Daru, there were areas of support – "the corners" – it came with stigma and unbalanced obligations.

At an institutional level, limited decentralisation of diagnostic and treatment services systematically disadvantaged rural populations. There was sophisticated understanding of this policy and system failure by many participants from rural areas. They voiced it as a rights-based issue that was resulting in gross inequities and were aware that governments were not doing enough. Participants were strongly advocating for change.

The policy implications are that there is an unmet and urgent need for decentralisation of TB services, and primary health care, outside of Daru. This is an enormous logistical and service delivery challenge – requiring investment in infrastructure, transport and communications - but one that needs to be met.

4.4.4 Household TB transmission dynamics

The interviews highlighted a critical, and unique contextual influence on the TB care journey and structural determinant of TB transmission - households in Daru. A systematic review and meta-analysis examined the individual and population impact of

household TB exposure on transmission. It found that households of TB index cases are areas of intense transmission, with children in households 3.79 times (95%CI 3.01-4.78) more likely to be infected than those in the community. However, at the population level, they estimated that only <20% of transmission was attributable to household exposure. While this suggests that most transmission occurs outside households globally, the extreme overcrowding and fluid boundaries observed in Daru may substantially increase the household contribution to transmission in this setting.

Due to cyclical and permanent migration from mainland villages to access services, including health, education and employment, households in Daru had significant overcrowding. Household composition included multi-generational kinship groups, with multiple family units. People were unable to implement separation when a person with infectious TB was in the house, facilitating transmission. This included exposure to high-risk groups for development of active TB following exposure – children under 5 years.

In addition, there were fluid household boundaries with movement between households to live with relatives for social reasons, but also occasionally due to conflict or violence. Migrants seeking TB care from mainland villages often had to negotiate for accommodation in Daru, compromising their safety and health and moved between dwellings.

These factors resulted in households being a key determinant of TB transmission, but also key for intervention. Due to overcrowding, households contacts of index TB cases in Daru are likely to be at higher risk of TB exposure. However, due to the fluidity and movement, substantial transmission may occur outside the household. Despite this fluidity, households remain an important societal unit that people identified with, given the kinship groups and association with corners.

Understanding these household dynamics proved essential for designing prevention interventions that could work within rather than against existing social structures, directly informing the household contact investigation approach implemented in the subsequent study (Chapter 5).

4.4.5 Strengths and limitations

The study had several strengths. First, local research assistants from Daru conducted interviews in both English and Kiwai, enabling participants to express themselves in their preferred language. The research team received comprehensive training in both research ethics and interview techniques, with ongoing supervision and mentorship

during data collection. Second, the purposive sampling strategy successfully captured a diverse range of experiences, including both drug-susceptible and MDR-TB patients, urban and rural residents, and equal gender representation. Third, the use of semi-structured interviews allowed for both consistent data collection across participants while enabling exploration of individual experiences. Finally, the study timing (2018) coincided with a period of established community-based TB care with a person-centred model, allowing insights into a functioning but still-evolving system.

However, there were several limitations. First, the study only captured the experiences of patients who were actively engaged in care, missing the perspectives of those who had discontinued treatment or never accessed services. Selection bias may have occurred as participants were initially approached by healthcare workers, potentially favouring those with more positive relationships with the health system. This also could have led to potential social desirability bias in participant responses, given the interviews were about a service they were currently receiving.

Second, the cross-sectional nature of the study, where interviews were conducted during a relatively short period (January-February 2018), limited the ability to observe changes over time. The sample size of 20 adult participants, while appropriate for qualitative research, may not have captured all relevant experiences, particularly from more remote communities, as interviews were only conducted in Daru. The study did not capture experiences of childhood TB within families. While participants were asked about children in their care, the interview guide did not include specific probes about children's TB illness or its impact, including on adult's care seeking, representing an important gap given the high childhood TB burden.

Finally, the unique socio-cultural context of Daru, especially the migration patterns and socio-economic disadvantage may not reflect experiences in other parts of Western Province or PNG.

4.5 Conclusion

This study provides critical insights into the lived experiences of people with TB in Daru, Papua New Guinea, revealing the complex interplay between individual, community and institutional influences on access and utilisation of care. The findings demonstrate that while biomedical interventions are essential, successful TB treatment is deeply embedded within socio-cultural and economic contexts that significantly influence patient outcomes.

The research highlights how treatment experiences are shaped by multiple intersecting factors: the crucial role of family support networks, the significant financial and geographical barriers to accessing care, and the variable quality of healthcare interactions. These factors operate within a broader context of resource constraints and complex household dynamics unique to the South Fly District setting.

These findings have important implications for TB program delivery. They suggest the need for more comprehensive support systems that address both medical and socio-economic barriers to treatment, particularly for patients from remote areas. The study also emphasises the importance of strengthening patient-provider relationships and adapting service delivery to local contexts. Future interventions should consider how to better leverage existing family and community support structures while addressing structural barriers to care – in particular poverty and financial hardship, nutritional support and importantly, decentralisation of services outside of Daru.

Structural interventions, while ambitious, such as housing development and planning in Daru need to be considered. Temporary accommodation for TB patients could be an interim solution. It was evident from these interviews that community demand for quality, accessible and equitable health services, including TB care was very high. There needs to be a major focus on more equitable resource allocation and greater political commitment to TB control and addressing its determinants at all levels of government.

Importantly, the complex kinship networks, fluid household boundaries, and high transmission risk within overcrowded living spaces highlighted the urgent need for systematic household-focused approaches such as contact investigation, to detect active TB early and identify those who would benefit from the provision of TPT. This research informed the development of the implementation study that is the focus of Chapter 5.

Combined biomedical and social interventions and approaches, with people and communities at the centre are essential for improving TB detection, treatment outcomes and advancing toward ending TB in high-burden settings.

Chapter 5: A prospective implementation study of community-based TB contact investigation in a high burden MDR/RR-TB setting in Papua New Guinea

This chapter presents a prospective implementation study of community-based household contact investigation in Daru from October 2017 to December 2020 that I designed and led with my primary supervisor. Building on the socio-ecological insights from Chapter 4, this study established the first systematic implementation of community-based contact investigation and TPT provision in PNG, including novel regimens and tuberculin skin testing for infection detection. The household engagement platform developed through this work and the operational frameworks and tools provided the foundation for expanding community-based prevention interventions beyond traditional facility-based approaches.

5.1 Introduction

Household contact screening and management for TB, or contact investigation, is universally recommended for active TB detection and the provision of TPT for high-risk individuals without disease.[159,167,483] Household TB contacts of an index case with bacteriologically positive TB are at risk of infection and developing active TB,[167] especially young child contacts (<5 years) who commonly develop disease within three months following exposure.[52] Therefore, child contacts should be investigated promptly and TPT initiated in those without disease, even if a test for infection is not feasible.[484]

However, despite strong evidence of effectiveness and safety of rifamycin and isoniazid based regimens (see Chapter 2), TPT for young child contacts is often not implemented in high TB burden settings, leading to excess preventable morbidity and death.[121,483] The global "prevention gap" is still very wide with TPT coverage far lower in young child contacts than it is for other high-risk eligible groups such as PLHIV.[280] Common barriers to improved coverage include a passive, facility-based approach to contact investigation as well as a lack of understanding by healthcare workers and families of the rationale for TPT which requires administering treatment daily to an asymptomatic child for up to six months.[122,485]

In PNG, childhood TB (in people <10 years) is very common, representing around 25% of notified cases, and a major cause of hospitalisation and mortality.[407,486] Many of these children with TB represent missed opportunities for early detection or prevention. The

coverage of contact screening and management, including TPT for young child contacts without active TB, is very low in PNG despite national recommendations and implementation is usually passive and centralised. PNG is also a high burden country for MDR/R-TB, with an unprecedented transmission hotspot in Daru, South Fly District, Western Province, where MDR/RR TB accounts for 32% of bacteriologically confirmed TB notifications (Chapter 3).[404,408] The WPHA and partners established a community-based model of care for the detection and treatment of active TB and MDR/RR-TB in 2014, resulting in improved treatment success from 53% in 2014 to consistently above 85% from 2016 onwards.[404]

The previous retrospective cohort study in Chapter 3 documented persistently high TB case notification rates in South Fly District, with alarming levels in Daru, and revealed that 20.7% of case notifications were in children (<15 years), with the proportion of cases in young children (0-4 years) increasing from 7.0% to 10.0% between 2014-2019. Several epidemiological factors, including the high TB burden in children and adolescents and high proportion of new cases among MDR/RR-TB, coupled with molecular epidemiology, indicate ongoing intense community transmission despite programmatic interventions for passive case detection and treatment. The next sequential step in building a comprehensive model was implementing a model of community-based screening through contact investigation, which had not been established in any setting in PNG.

Community-based contact investigation was introduced in Daru in 2016, initially screening for active disease in household contacts of all ages of people with bacteriologically confirmed MDR/RR-TB.[397] This was then extended to household contacts of drug-susceptible (DS) TB index cases in 2017 with the introduction of TPT for well, young child (<5 years) contacts using six months of daily isoniazid (6H or isoniazid preventive treatment, IPT) as per national guidelines at the time. A previous evaluation reported on this model of contact investigation over the two-year period from March 2016 to March 2018 (see Figure 5.1 for timeline).[397]

Based on updated WHO recommendations,[283] novel approaches were introduced in Daru in 2019 that include: a shorter TPT regimen of three months duration for young child DS contacts that uses a child-friendly formulation; testing for infection in contacts without active disease; and TPT in young contacts of MDR/RR-TB cases with evidence of infection. This study aimed to evaluate the expanded implementation of community-based contact investigation, including these novel approaches, and to report the

prevalence of TB disease and infection in household contacts of DS and MDR/RR-TB index cases and evaluate the implementation of TPT regimens for young child contacts.

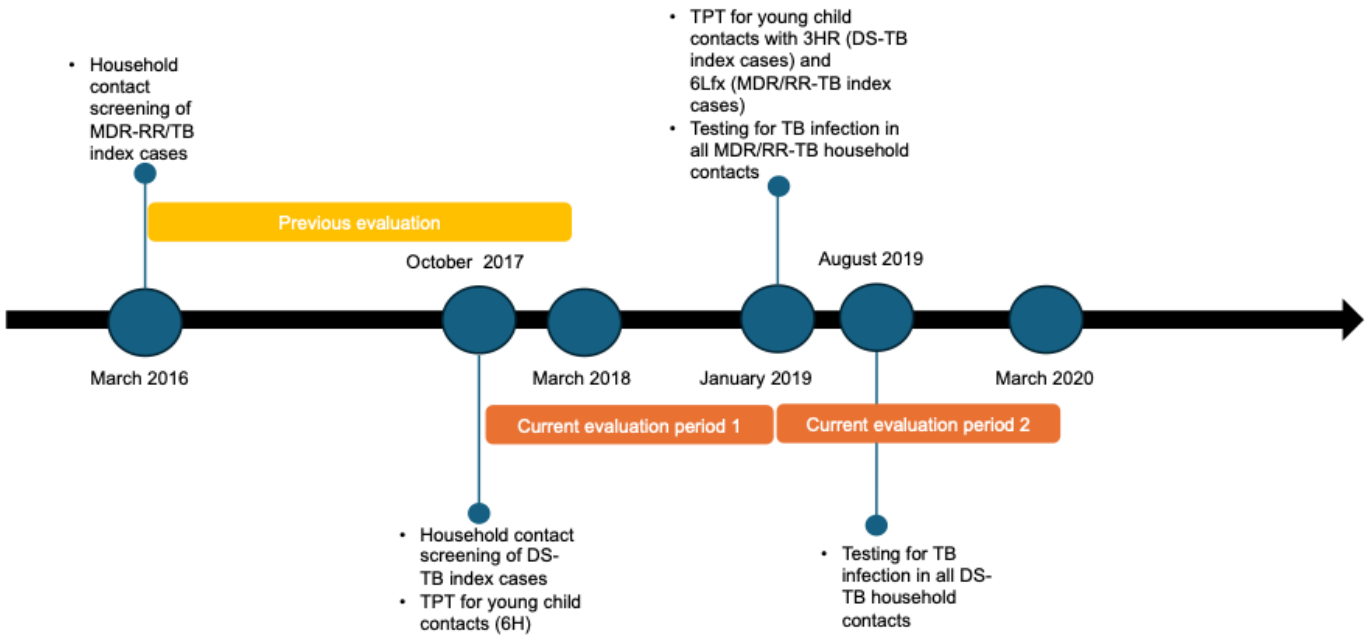
5.2 Materials and methods

5.2.1 Study design and setting

This prospective study was embedded with the routine WPHA TB program and conducted to evaluate the implementation of a community-based household contact investigation program on Daru between October 2017 and December 2020. The setting, household characteristics and model of care have been described in detail in Chapters 1, 3 and 4.

The steps taken to introduce and establish a household contact investigation on Daru from March 2016 have been described in detail in our previous publication (Honjepari et al.) along with a retrospective evaluation.[397] Contact evaluation for active TB involved referral of individuals to the DPH for medical officer review and a TPT clinic for eligible young children. In October 2017, community-based contact clinics for evaluation and IPT initiation for eligible young children were established. These clinics were established in the existing ambulatory DART sites.

Figure 5.1 Timeline for contact investigation and management interventions and evaluations in Daru, PNG



DS: drug-susceptible, MDR/RR: multidrug/rifampicin-resistant, TPT: TB preventive treatment, H: Isoniazid, HR: isoniazid and rifampicin, Lfx: Levofloxacin

5.2.2 Study population, period and interventions

The study population was household contacts of people with recently diagnosed bacteriologically confirmed DS- and MDR/RR-TB who were resident on Daru, PNG. Household contacts were defined as any person who lived in the same house as the index case within three months prior to diagnosis, including those who regularly spent time in the house without residing there. Due to the fluid household dynamics (described in Chapter 4), contacts were often screened across several adjacent houses where a family group lived and there was potential exposure, fitting the above criteria.

This study evaluated findings from contact investigation activities for a 30-month period- from 1st October 2017 until March 31st 2020, when activities were disrupted by the COVID-19 pandemic. Figure 5.1 displays the timeline of contact investigation interventions including the previous evaluation period (January 30th 2016 to March 31st 2018) and the current evaluation which is described in two study periods each of 15 months duration.

In the first period (October 1st 2017 to 31st December 2018), 6H was used as TPT in young child DS-TB contacts. During the second period (January 1st 2019 to March 31st 2020) novel approaches were introduced from January 2019 for implementation and evaluation:

(i) Three months of daily oral isoniazid and rifampicin (3HR) replaced six months of daily isoniazid as TPT for young child contacts of DS-TB. A dispersible, fixed-dose combination of HR replaced isoniazid tablets as the child-friendly formulations of first-line TB drugs for young children had become available in PNG for treatment of DS TB.[10] The change to 3HR was supported by evidence of similar efficacy but improved safety and adherence compared to 6H.[283,487]

(ii) Six months of daily oral levofloxacin (6Lfx) was introduced as TPT for young child contacts of MDR/RR and fluoroquinolone-susceptible TB cases, who had evidence of infection after active disease was excluded. The choice of regimen was supported by observational evidence of benefit and safety,[159,488,489] with these findings since supported by evidence from randomised placebo-controlled trials.[489,490]

(iii) Testing for TB infection was introduced for all household contacts aged five years or older without active TB to determine the prevalence of infection and inform future approaches for management. This was conducted initially for MDR/RR TB contacts only and then introduced for DS-TB contacts in August 2019, as resources allowed. While in 2018, WHO had made a new conditional recommendation to expand TPT to HIV-negative household contacts 5 years and older without active TB,[283] PNG had not adopted this recommendation at the time of this study. Participants over 5 years who had TB infection, but no active disease were informed of their potential increased risk of developing active TB and educated on how to seek TB diagnosis and care should symptoms develop.

5.2.3 Study procedures

The following procedures describe both the routine programmatic implementation of contact investigation and the research components designed to evaluate these interventions. Data collection for research purposes was integrated into routine program operations, with three additional local staff recruited (a research nurse and health promotors).

In preparation for implementation of the new TPT regimens (3HR, 6Lfx), in late 2018, additional and expanded community engagement and education activities were conducted. This included community forums and media (radio and TV) with a focus on explaining TB infection (called “sleeping TB”) and the potential benefits of TPT. The model of patient education and counselling previously developed for active TB care[150] was adapted as family-centred approach for young child contacts eligible for TPT and their guardians and families. Communication tools to explain “sleeping TB” and TPT included visual aids and participatory activities in local language. Standardised education materials and counselling sessions were used to obtain informed consent for TST and novel TPT regimens. The community treatment sites were established as “child-friendly” spaces using a family-centred approach to support the care and treatment of young children on TPT.

Contact screening and management for all recently diagnosed bacteriologically confirmed (pulmonary or extrapulmonary) TB were provided by a team of nurses and community health workers (a formal cadre in PNG), led by a health extension officer (HEO, an auxiliary medical officer) and under the supervision of a medical officer, in a community-based model of care following standard operating procedures. Trained health

promoters (a community health worker) were responsible for community engagement and participant education and consent using local language. Following verbal consent by index cases or their guardian and the household head, contact screening occurred at the household level and often included multiple adjacent households or extended family groups. This screening beyond a single household was determined by the community engagement teams in consultation with the families screened, household heads and/or local leaders. A nurse was responsible for training, administration and reading of the tuberculin skin test (TST), as described below. The contact screening team aimed to conduct screening and TST placement within two weeks and up to one month from diagnosis of an index case. Up to three additional household visits within a month were performed to facilitate investigation of all contacts. Break of contact screening was not performed.

Individual contacts were tracked using the cascade of care approach for case detection and TB prevention where individuals move through the health system for case detection and TB prevention.[290] A paper-based household mapping tool (HMT), which was adapted after successful use by a number of Daru staff in another setting,[491] was used by the contact investigation team for care and was the basis for data collection for evaluation. The HMT and key study tools that were developed are in Appendix 5.1.

All potential household contacts were recorded on the HMT and were screened for the presence of one or more TB-related symptoms to identify active TB: persistent (>2 weeks) cough, fever or night sweats, evidence of extrapulmonary such as enlarged visible lymph nodes, weight loss or severe undernutrition in young children. Young child contacts were screened for nutritional status, as per WHO guidelines.[492] Nutritional status was determined according to PNG guidelines using mid-upper arm circumference (MUAC) in children aged 6 to 60 months weight-for-age for children under six months. Malnutrition defined as moderate by a MUAC between 11.5 and 12.5cm or weight or age WHO z-score -2 to -3 and severe by a MUAC <11.5cm or WHO z-score below -3. Malnutrition was managed according to local guidance with nutritional supplementation and empiric treatment for soil transmitted helminths with albendazole as well as evaluation for active TB.

Evaluation for active disease

Contacts with a positive symptom screen (presumptive TB) were referred to the TB diagnostic clinic for further clinical evaluation including chest radiography and microbiological confirmation, as per local guidelines and previously described.[404] Sputum was collected when able to be produced for acid-fast bacilli smear microscopy and Xpert

MTB/RIF assay with Xpert Ultra introduced in 2019. If sputum could not be produced or tested negative for TB, further evaluation may have involved gastric aspirate for Xpert MTB/RIF and/or other investigations for extrapulmonary TB as appropriate, such as fine needle aspirate of enlarged lymph nodes or stool sample for Xpert MTB/RIF. Persons diagnosed with TB were registered and treatment for TB commenced according to drug susceptibility using program protocols, including HIV testing. Contacts were not systematically tested for HIV. Those who self-identified or were known to be HIV-infected by the clinical staff were referred to the HIV clinic at Daru Provincial Hospital for care and initiation of isoniazid preventive treatment (6H), as per national guidelines.

Evaluation for TPT

The household head and all contacts (or their parent/guardian if under 18 years) were informed of the study and asked to provide assent and written informed consent, respectively for TST (for contacts without presumptive or active TB) and the novel TPT regimens (3HR or 6Lfx) for eligible young child contacts. If the study team assessed the participant as unable to read or understand consent or write, a support person, guardian or carer could support consent. Education and informed consent were offered in the appropriate local language-English, Tok Pisin or Kiwai. The participant information and consent forms are displayed in Appendix 5.2

If they declined participation in the study, routine standard of care as per PNG guidelines continued with screening and 6H was offered for eligible contacts. In those who consented, the study nurse performed a TST on contacts who screened negative at the initial home visit. Contacts who screened positive, but later had active TB excluded, were offered TST at a follow-up visit. TST was performed according to international guidelines with intradermal injection of 0.1 ml tuberculin purified protein derivate (PPD, Tubersol 5TU, Sanofi Pasteur) and read 48-72 hours post injection. TST was considered positive when the transverse diameter of induration was ≥10 mm, regardless of BCG vaccination status. Tubersol was procured from City Pharmacy Limited (Port Moresby), PNG's largest private pharmacy and a medical supply company with quality assurance and cold-chain procedures during transportation and storage.

TPT monitoring and care

Young child contacts eligible for TPT – asymptomatic or active TB excluded in those who were symptom screen positive - were referred and supported to attend the weekly “sleeping TB” clinic which was established at the nearest community treatment sites. The HEO conducted a further a clinical review and determine eligibility for TPT.[287] Dosing for

6H was as per PNG national guidelines. Dosing for the newer regimens was as per WHO guidelines for 3HR and the clinical trial protocols for current studies evaluating 6Lfx.[484,490] A parent or guardian was educated regarding medication preparation, dosing and administration. If initiated, home-based self-administered treatment with monthly review at the clinic was provided. The assessments involved clinical review by the HEO – rescreening for TB, weight, adverse effects – and review of medication, adherence through pill count and provision of the next months' supply. Standardised education on TPT is provided by community-based nurses at the sleeping TB clinic at baseline and two-month follow-up with support from the counselling team as needed to address barriers to adherence.

TPT outcomes were reported for individuals who were prescribed and took at least 1 dose. The outcomes assigned were complete, loss to follow-up (LTFU, defined as interrupted treatment for ≥ one consecutive month for 3HR and ≥ two months for 6Lfx), developed active TB during TPT (failed), died, treatment discontinued (by clinician) or transferred out. Follow up was planned between month 6 and 12 post completion of TPT to assess disease-free status. Program-based active drug safety monitoring for possible adverse events associated with the use of the newer TPT regimens was conducted at monthly reviews. Specific laboratory monitoring was not required at baseline or during therapy. The severity of adverse events was graded by the HEO using the NIH Division of AIDS (DAIDS) table for grading the severity of adult and paediatric adverse events standard table as recommended by WHO and in the PNG programmatic management of DR-TB (PMDT) study standard operating procedure (SOP) for the use of new and repurposed TB drugs.[493] National Department of Health and ethics committee reporting requirements for severe adverse event (SAE) reporting were established.

Contacts with positive TST but not eligible for TPT (age ≥5 years and HIV-negative) were informed of their status of having TB infection and counselled regarding the result. Contacts exposed to an index case with fluoroquinolone resistance were not offered TPT and counselled. These groups were provided education regarding symptoms of TB disease and the importance of early presentation to health services.

All procedures were documented in a SOP available in Appendix 5.3.

5.2.4 Data collection and analysis

Data were entered from the paper-based household mapping tool, TPT enrolment and treatment cards (Appendix 5.1) into the WPHA TB program electronic medical record

system (EMRS, Bahmni v.0.87; Thought works, Chicago, IL, USA), which was part of the routine TB program and configured to have a TPT module. Data on TB diagnosis and treatment were entered in the EMRS routinely. Variables collected for cases and contacts included age, gender, primary residence and TB clinical information (site, resistance, bacteriological confirmation and registration category) and HIV status for cases. The data were extracted from the EMRS using automated scripts and imported into Stata v.15 (StataCorp, College Station, TX, USA) and R v.3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) with v.1.2.1 of the tidyverse package for validation checks and analysis. Categorical variables were described by frequency and proportion, and continuous variables by median and interquartile range.

Two TB care cascades have been evaluated, the TB case detection cascade and the TB prevention cascade. The cascade of care for detection for household contacts described the steps of identified (enumerated and listed on the HMT), screened (for symptoms), screened positive, active TB diagnosed (clinical or bacteriologically confirmed, co-prevalent or incident), treatment initiated and completed treatment, disaggregated by age group. The “yield” of contact investigation for (TB treatment register) active TB, or cumulative incidence, was defined as the proportion of the number of new bacteriologically confirmed cases and clinically diagnosed in household contacts among those screened. The bacteriologically confirmed yield is also calculated. Co-prevalent TB among household contacts was defined as a diagnosis within 90 days of household screening, allowing time for evaluation. Incident TB was defined as a diagnosis between 91 and 360 days of screening. The TB prevention cascade described the steps of contacts identified, screened, active TB diagnosed, TST placed and positive, eligible for TPT (TST positive, no active TB), TPT commenced by regimen; disaggregated by index case resistance profile (TB treatment register).

The prevalence of TB infection among household contacts without co-prevalent active TB was calculated as a proportion of TST positive among those read. Data were collected and entered prospectively through the study period. As the use of TPT and TST changed during the study period along with requirements for informed consent, a sub-analysis was done which compared period 1, when 6H was used in young child DS TB contacts to the second when 3HR replaced 6H and 6Lfx was introduced along with TST to determine eligibility and prevalence among contacts.

5.2.5 Ethics

Ethical approval was obtained from the Medical Research Advisory Committee, PNG (MRAC 18.08) and the Alfred Hospital Ethics Committee, Australia (5/19), specifically for the introduction and evaluation of the novel approaches to contact investigation, which were outside PNG guidelines at the time (2018-2019) and testing for TB infection in household contacts not eligible for TPT.

5.3 Results

During the 30-month study period (see Figure 5.1), contact investigation was conducted for 617 index cases with bacteriologically confirmed TB, of which 439 had DS-TB and had 176 MDR/RR-TB. Their characteristics are displayed in Table 5.1 and by study period. The coverage of contact investigation among notified bacteriologically confirmed TB index cases was 73.7% overall, 71.1% for DS-TB and 81.2% for MDR/RR-TB index cases. There were more index cases in the second study period (January 2019 to March 2020) with a greater proportion of males, children and young adolescents, extrapulmonary TB and people from Daru (noting the reduced unknown residence category).

A total of 5,537 household contacts of bacteriologically confirmed index cases were identified and 19.0% were young children (< 5 years). Of these, 4,988 were screened (investigated) resulting in a contact investigation coverage of 90.1% for all ages and 90.8% for young children. The median (IQR) number of contacts per index case was 12 (8,17), with higher numbers for MDR/RR-TB index cases (median 13, IQR 9-22) compared to drug-susceptible TB (median 11, IQR 8-16). The overall characteristics of the contacts and by study period are displayed in Table 5.2, with no major differences other than a greater proportion from Daru in period 2. Of the 954 contacts under 5 years, 436 (45.7%) had nutritional status recorded. Malnutrition was present in 15.8% (4.1% severe, 11.7% moderate) and 2.3% were overweight. High quality data on BCG history in household contacts in Daru were not available. Annual birth dose BCG coverage in SFD was 64% (2017), 21% (2018), 48.4% (2019) and 40.9% (2020), respectively (WPHA data).

The cascade for detection and treatment of all forms of TB (bacteriologically confirmed and clinically diagnosed) is presented in Table 5.3. Of the 4,988 contacts screened, 962 (19.3%) screened positive for TB symptoms. Following evaluation of those who were symptom-screen positive, 154 (16.0%) were diagnosed with active TB and initiated on treatment and 142 (92.2%) completed treatment successfully. The treatment success

(completion) was very high; 92.4% for DS-TB and 91.4% for MDR/RR-TB and was higher for children <15 years compared with adults.

The contact screening yield (proportion of contacts with bacteriologically confirmed TB among household contacts within 360 days from screening) was 3.2% (159/4,988) overall, including both bacteriologically confirmed and clinically diagnosed cases. This equates to a number needed to screen of 31 household contacts to detect 1 case of active TB. The contact screening yield for co-prevalent TB (TB diagnosed within 3 months of screening) was 1.4% and for incident TB (diagnosed between 3 and 12 months after screening) was 1.8%. The highest screening yield was in young children (6.5% for all forms of TB) and the majority of these were co-prevalent TB. Most cases detected in contacts were incident TB in all age groups except for young child contacts.

When restricted to bacteriologically confirmed cases only, the yield was 1.3% (67/4,988), with 0.5% for co-prevalent TB and 0.8% for incident TB (see Appendix 5.4 for detailed TB case detection cascade table for bacteriologically confirmed active TB). This equates to a number needed to screen of 74 household contacts to detect 1 case of bacteriologically confirmed TB. The bacteriologically confirmed screening yield in young children was 0.6%. The difference in overall yield between all forms (3.2%) and bacteriologically confirmed TB (1.3%) is largely driven by clinical diagnosis in young children, where 90.3% of cases (56/62) were clinically diagnosed compared to 52.6% in 5-14 years, 26.9% in 15-34 years, 39.1% in 35-54 years, and 50.0% in those ≥55 years.

There were 35 contacts diagnosed with MDR/RR-TB and 124 with DS-TB with a similar distribution across the two periods, 56.5% were diagnosed in period 1. Overall, 11.6% of contacts were screened more than once and 13.2% of contacts had two or more index cases. There were 135 contacts (2.7%) who had both DS and MDR-TB index cases. The concordance (proportion of contacts with active TB where the resistance profile was the same as their index case) was 51.4% for MDR/RR-TB, 87.4% for DS-TB and 75.3% overall.

The TB prevention cascade for children under 5 years is shown in Table 5.4. Of the 874 child contacts who were screened and did not have active TB, 76.0% were eligible for TPT, of which 51.8% commenced treatment. This included 12 young child contacts of MDR-TB index cases who were TST positive and therefore eligible for TPT.

The treatment outcomes for the 354 young child contacts who commenced TPT are listed in TST: tuberculin skin test; H: isoniazid; HR: rifampicin and isoniazid; Lfx: levofloxacin

Table 5.5. All contacts who commenced TPT with 6Lfx completed treatment. LTFU and treatment completion were similar when comparing 6H and 3HR with slightly higher treatment discontinuation in the 3HR group (8.0% vs 4.4%). Treatment was discontinued in 20 contacts, among whom 12 discontinued due to adverse events. Of the 8 discontinuations not related to adverse events, 5 were patient decisions and 3 were clinician decisions.

There were 19 adverse events reported in participants, 11 on 6H and 8 on 3HR. All were grade 1 or 2 and involved rash, neurological (behavioural) or gastrointestinal events. No serious adverse events were suspected or reported. Due to the COVID-19 pandemic and impacts on TB human resources and research staff, systematic follow-up of the study participants who completed TPT to determine TB status at 6 months was not completed.

Of the 4,829 household contacts without active TB, TST was performed in 885 (18.3%) of whom 329 (37.0%) had DS-TB index cases, and 556 (62.8%) had MDR/RR-TB. Among the MDR-TB contacts, 72 (8.1%) also had a DS-TB index case. The overall prevalence of infection was significantly higher among MDR/RR contacts, 49.4% (266/556) compared to 36.8% (121/329) among DS-TB contacts (p=0.001). Figure 5.2 shows the age-stratified prevalence of TB infection among household contacts, without active TB, by index case resistance profile. The proportion of young child contacts (0-4 years) with evidence of infection was 10.8% overall but was significantly higher in contacts of MDR/RR (15.8%) compared with DS-TB (1.7%) index cases (P<0.05). The prevalence of TB infection increased with increasing age of contacts up to a peak in the 35-54 years age group (69.8% for DS-TB and 78.7% for MDR/RR-TB) and was lower in the older adult age groups. Figure 5.3 displays TB infection prevalence in contacts by the index case resistance profile and gender. Child contacts (0-14 years) who had a female index case had a higher prevalence of TB infection. Data on index case bacterial load or disease burden were not available for this study.

Table 5.1 Characteristics of index TB cases of contacts screened during by study period in Daru, PNG, October 2017 – March 2020

	October 2017–December 2018 Period 1		January 2019 – March 2020 Period 2		Total		
Characteristic	n	%	n	%	n	%	p-value[1#^]
Total screened	254	(41.2%)	363	(58.8%)	617		
Notified cases (coverage %)	401	(63.3%)	433	(83.8%)	834	(74.0%)	
Age group							
Median (IQR)	28	(18,39)	25	(18,37)	25	(18,38)	0.13
0 – 4	4	(1.6%)	13	(3.6%)	17	(2.8%)	0.06
5 – 14	16	(6.3%)	48	(13.2%)	64	(10.4%)	
15 – 34	149	(58.7%)	196	(54.0%)	345	(55.9%)	
35 – 54	65	(25.6%)	81	(22.3%)	146	(23.7%)	
≥ 55	20	(7.9%)	25	(6.9%)	45	(7.3%)	
Female	135	(53.1%)	167	(46.0%)	302	(48.9%)	0.08
Resistance[2]							
DS-TB	181	(71.3%)	260	(71.6%)	441	(71.5%)	0.5
MDR/RR	66	(26.0%)	92	(25.3%)	158	(25.6%)	
FQ-R	7	(2.8%)	11	(3.0%)	18	(2.9%)	
Disease site							
Pulmonary	215	(84.6%)	269	(74.1%)	484	(78.4%)	0.002
Extrapulmonary (only)	39	(15.4%)	94	(25.9%)	133	(21.6%)	
HIV Status							
Negative	247	(97.2%)	345	(95.0%)	592	(95.9%)	0.4
Positive	4	(1.6%)	8	(2.2%)	12	(1.9%)	
Unknown	3	(1.2%)	10	(2.7%)	13	(2.1%)	
Registration							
Newly diagnosed	224	(88.2%)	316	(87.1%)	540	(87.5%)	0.9
Previously treated	30	(11.8%)	46	(12.7 %)	76	(12.3%)	
Not recorded	0	(0%)	1	(0.3%)	1	(0.2%)	
Primary Residence							
Daru	158	(62.2%)	274	(75.5%)	432	(70.0%)	<0.001
Outside Daru	6	(2.4%)	45	(12.4%)	51	(8.3%)	
Unknown	90	(35.4%)	44	(12.1%)	134	(21.7%)	

IQR: interquartile range; DS-TB: drug-susceptible TB; FQ-R: fluoroquinolone-resistant TB

[1]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

[2]Clinician assessed resistance profile from genotypic and/or phenotypic testing. Resistance was not recorded in 11 patients, 2 in period 1 and 9 in period 2–these were assumed to be DS-TB

Table 5.2 Characteristics of household TB contacts screened by study period in Daru, PNG, October 2017 – March 2020

Characteristic	October 2017 – December 2018 Period 1		January 2019 – March 2020 Period 2		Total		
	n	%	n	%	n	%	p-value[1]
Total	2,408	(48.3%)	2,580	(52.1%)	4,988		
Age							
Median (IQR)	18	(6, 37)	17	(7, 35)	18	(6, 36)	
0 – 4	490	(20.3%)	463	(17.9%)	953	(19.1%)	<0.001
5 – 14	510	(21.2%)	594	(23.0%)	1,104	(22.1%)	
15 – 34	743	(30.9%)	865	(33.5%)	1,608	(32.2%)	
35-54	387	(16.1%)	438	(17.0%)	825	(16.5%)	
≥ 55	273	(11.3%)	220	(8.5%)	493	(9.9%)	
Unknown	5	(0.2%)	0	(0.0%)	5	(0.1%)	
Female	1,179	(49.0%)	1,283	(49.7%)	2,462	(49.4%)	0.6
Index case resistance							
DS-TB	1,654	(68.7%)	1,852	(71.8%)	3,506	(70.3%)	<0.001
MDR/RR-TB	659	(27.4%)	688	(26.7%)	1,347	(27.0%)	
Both	95	(3.9%)	40	(1.6%)	135	(2.7%)	
No. index cases linked							
1	2,009	(83.4%)	2,325	(90.1%)	4,334	(86.9%)	<0.001
2	307	(12.7%)	165	(6.4%)	472	(9.5%)	
3	60	(2.5%)	83	(3.2%)	143	(2.9%)	
4	28	(1.2%)	7	(0.3%)	35	(0.7%)	
5	4	(0.2%)	0	(0.0%)	4	(0.1%)	
Primary Residence							
Daru	1,880	(78.1%)	2,399	(93.0%)	4,279	(85.8%)	<0.001
Outside Daru	493	(20.5%)	171	(6.6%)	664	(13.3%)	
Unknown	35	(1.5%)	10	(0.4%)	45	(0.9%)	

IQR: inter-quartile range, DS: drug-susceptible TB, MDR/RR-TB: multidrug and/or rifampicin resistant TB

[1]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 5.3 TB case detection cascade for household contacts by age group, Daru, PNG, October 2017 – March 2020

	0-4		5-14		15-34		35-54		≥55		Total	
Identified	1,051		1,229		1,133		885		607		5,537	
Screened (% identified)	954	(90.8%)	1,103	(89.7%)	1,032	(91.1%)	825	(93.2%)	493	(81.2%)	4,988	(90.1%)
Screened Positive (% screened)1	247	(25.9%)	228	(20.7%)	132	(12.8%)	164	(19.9%)	103	(20.9%)	962	(19.3%)
Active TB (% screened positive, all forms)[2]	62	(25.1%)	19	(8.3%)	26	(19.7%)	23	(14.0%)	14	(13.4%)	159	(16.5%)
Co-prevalent TB (% active TB)[3]	33	(53.2%)	6	(31.6%)	9	(34.6%)	6	(26.1%)	6	(42.9%)	67	(42.1%)
Incident TB (% active TB)[4]	29	(46.8%)	13	(68.4%)	17	(65.4%)	17	(73.9%)	8	(57.1%)	92	(57.9%)
DS-TB (% active TB)	48	(77.4%)	14	(73.7%)	21	(80.8%)	20	(87%)	13	(92.9%)	124	(78%)
MDR/RR-TB (% active TB)	14	(22.6%)	5	(26.3%)	5	(19.2%)	3	(13%)	1	(7.1%)	35	(22%)
Treatment initiated	57	(91.9%)	19	(100%)	26	(100%)	23	(100%)	14	(100%)	154	(96.9%)
Completed Treatment	55	(96.5%)	19	(100%)	23	(88.5%)	19	(82.6%)	12	(85.7%)	142	(92.2%)
Screening yield (all forms)[5]	62	(6.5%)	19	(1.7%)	26	(2.5%)	23	(2.8%)	14	(2.8%)	159	(3.2%)
Screening yield (bacteriologically confirmed)	6	(0.6%)	9	(0.8%)	19	(1.8%)	14	(1.7%)	7	(1.4%)	67	(1.3%)

DS-TB: drug-susceptible TB; MDR/RR-TB: multidrug and/or rifampicin resistant TB

[1]Screened positive = symptom screening

[2]Active TB = bacteriologically confirmed and clinically diagnosed TB diagnosed within 12 months of screening

[3]Active TB diagnosed within 90 days of household screening

[4]Active TB diagnosed between 91 and 360 days of household screening

[5]Active TB / screened

Table 5.4 TB prevention cascade by period for young child contacts, Daru, PNG, October 2017–March 2020

	DS-TB		MDR/RR-TB		Total	
Identified	786		265		1,051	
Screened (% identified)	722	(91.9%)	232	(87.5%)	954	(90.8%)
Active TB with 12 months (% screened)	50	(6.9%)	12	(5.2%)	62	(6.5%)
Not active TB (% screened)	672	(93.1%)	220	(94.8%)	892	(93.5%)
TST Placed (% not active TB)	-	-	101	(45.9%)	-	-
TST Positive, ≥10mm (% TST placed)	-	-	12	(11.9%)	-	-
TPT eligible (% of screened)	672	(93.1%)	12	(5.2%)	684	(71.7%)
TPT commenced (% of eligible)	342	(50.9%)	12	(100.0%)	354	(51.8%)
6H (%TPT commenced)	205	(60.0%)	-	-	205	(57.9%)
3HR (%TPT commenced)	137	(40.1%)	-	-	137	(38.7%)
6Lfx (%TPT commenced)	-	-	12	(100.0%)	12	(3.4%)

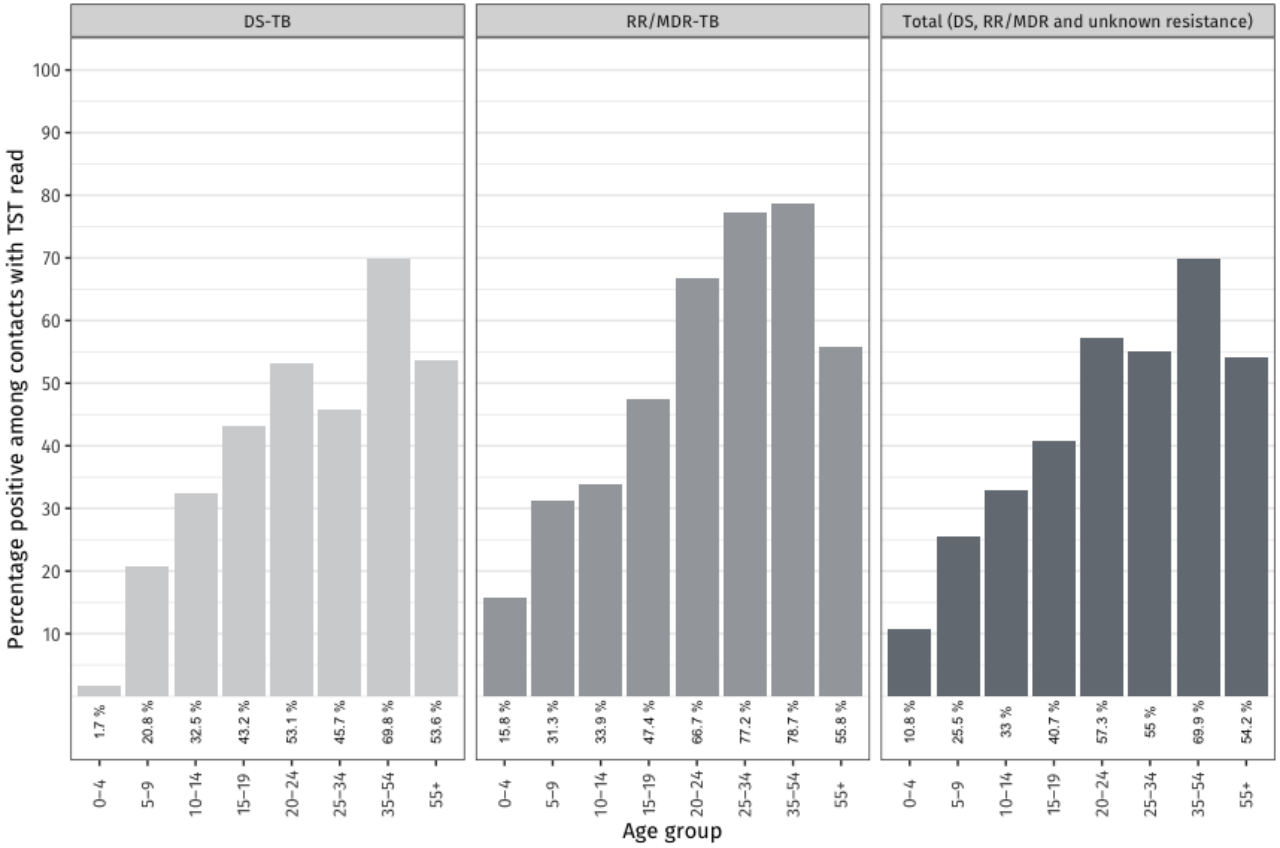
TST: tuberculin skin test; H: isoniazid; HR: rifampicin and isoniazid; Lfx: levofloxacin

Table 5.5 TPT outcomes for young child contacts, by regimen, Daru, PNG, October 2017–March 2020.

Regimen	**Complete**	**LTFU**	**Treatment discontinued**	**Transferred out**	**Total**
6H	170 (82.9%)	21 (10.2%)	9 (4.4%)	5 (2.4%)	205
3HR	113 (82.5%)	13 (9.5%)	11 (8.0%)	0 (0.0%)	137
6Lfx	12 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12
Total	295 (83.3%)	34 (9.6%)	20 (5.7%)	5 (1.4%)	354

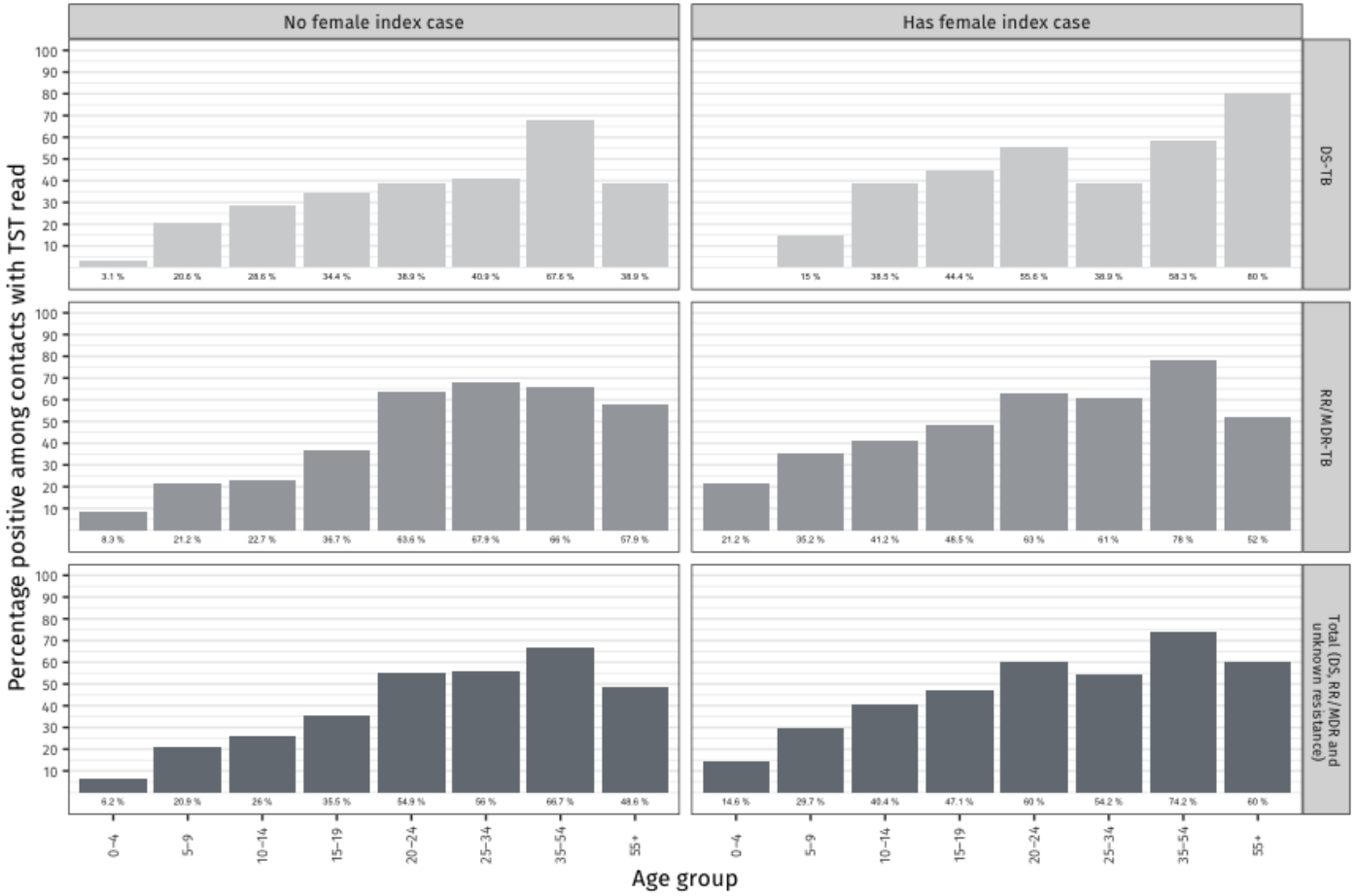
H: isoniazid, HR: isoniazid and rifampicin, Lfx: levofloxacin. LTFU: lost to follow up

Figure 5.2 Prevalence of TB infection in household contacts in Daru, 2019-20 by index case resistance profile



DS: drug-susceptible, MDR/RR-TB: multidrug and/or rifampicin resistant TB, TST: tuberculin skin test, TST positive: ≥10mm read at 48-72 hours.

Figure 5.3 Prevalence of TB infection in household contacts in Daru, 2019-20 by index case resistance profile and gender



DS: drug-susceptible, MDR/RR-TB: multidrug and/or rifampicin resistant TB, TST: tuberculin skin test, TST positive: ≥10mm read at 48-72 h

5.4 Discussion

This was a prospective study evaluating the implementation of a model of community-based household contact investigation in Daru, PNG. It showed a high co-prevalence and incidence of active TB among contacts, and moderate uptake and high completion and tolerability of TPT in young children using the newer regimens of 3HR and 6Lfx. This is the second report of household TB contact investigation in PNG, and is notably from a low-resource, remote and high MDR-TB burden setting using a community-based model for contact investigation. This study showed a high prevalence of TB infection among household contacts, which was low in the 0-4 age group, but increased with age-most markedly in older adolescents and young adults. The prevalence of TB infection was higher in household contacts of MDR-TB index cases, compared with those of DS-TB index cases.

5.4.1 TB detection and prevention

The yield of screening household contacts for all forms of TB of 3.2% and 1.3% for bacteriologically confirmed TB is comparable to a meta-analysis of contact investigation in LMICs, reporting a pooled yield of 2.87% (2.61–3.14) and bacteriologically confirmed active TB 2.04% (1.77–2.31).[241] However, our finding was lower than global meta-analyses, including MDR-TB; for example Velen et al. reported a pooled prevalence of 3.6% (3.3–4.0%) and 3.2% (2.6-3.7) for bacteriologically confirmed active TB.[342,494,495] The substantial heterogeneity across studies in these meta-analyses (I^2 >97%) demonstrates that contact investigation yields vary considerably between settings, reflecting the importance of local epidemiological and operational context.

The difference between bacteriologically confirmed (1.3%) and all forms of TB yield (3.2%) was predominantly driven by clinical diagnosis in young children, where 90.3% of cases were clinically diagnosed compared to 50-73% in older age groups. During the study period, there was a focus on high-quality child TB diagnosis, with clinical assessment prioritised when bacteriological confirmation was not feasible. This included dedicated paediatric expertise, training and case discussion with international experts, [496] providing confidence that clinical TB diagnosis reflected WHO-recommended practice rather than over-diagnosis (see Appendix 5.3 Standard Operating Procedures).

The high yield of incident TB in Daru, particularly in household contacts over 5 years, is notable, as cross-sectional studies often miss this group. This suggests that there may be considerable benefit at both the individual and community levels in Daru to prevent

active TB through screening and treatment, and potentially TPT in older household contacts, as recommended more recently by WHO.[497] Contact screening yield was highest in young children and was mainly co-prevalent TB, which is consistent with several studies and a paediatric meta-analysis as the highest risk group.[52,280,498] No young child developed active TB while receiving TPT, demonstrating the effectiveness of symptom screening-based models, without chest radiography in this age group.[121] Lower screening completion in contacts aged ≥55 years (81% vs ~90%) may reflect household absence during daytime screening, as older adults remained active in community work and social activities.

As progression to disease can be rapid, and TB mortality rates are high among young children, there is major benefit from the provision of TPT and birth dose BCG to this group.[435] BCG coverage rates in South Fly during the study period were low due to stock-outs and human resource constraints and is a priority for corrective action. While TPT for young children has been a long-standing recommendation and is routine in HICs, implementation has been limited and is yet to be systematically implemented in many LMICs, including PNG.[91] A recent cluster-RCT conducted in two African countries demonstrated the effectiveness of community-based screening and TPT provision by community healthcare workers for young child contacts of DS-TB index cases, over facility-based care.[253] While observational studies have reported on TPT uptake and completion in young child contacts, relatively few studies have previously reported the use of levofloxacin as TPT for MDR-TB contacts in LMICs.[444,488,489]

The moderate uptake of TPT in DS-TB contacts was likely due to several factors noted by the contact investigation team – movement of families out of Daru, loss during the diagnostic evaluation process (if TB was excluded, the child may not have been referred or reached for TPT provision) and acceptance by the appropriate parent or guardian. A lesson from this study was that in some instances, consent was needed to be obtained from both parents, and/or assent was needed from the household head. In our previous work[397] and early in this study it was observed that levels of understanding of TB infection and benefit of TPT were low and therefore family-centred education and counselling materials and models were developed.[94,397] Despite this engagement, if TB care and services are only available in Daru, this becomes a major barrier for many families who travel to mainland villages.[152] However, as is the case for treatment of active TB, treatment outcomes are usually successful once patients and families make a decision to initiate treatment.[404] The community-based, family-centred model of care with patient education and counselling in Daru was a likely contributor to the high TPT completion

rates.[94,150] The high uptake and completion of TPT in young child MDR/RR-TB contacts compared with DS-TB, noting the small cohort, was likely due to greater attention and education provided to families in this group, however further qualitative research to understand the barriers and enablers for TPT acceptance and completion would be informative in this setting.

The high rates of TPT completion among those who commenced treatment and excellent tolerability (low adverse events) with the newer regimens were consistent with other studies in young children- implementation of 3HR in four African countries,[499] and the results of the TB-CHAMP clinical trial for 6Lfx.[500] A meta-analysis of TPT regimens has shown that the rifamycin-based TPT regimens (including 3HP and 1HP) have lower adverse events and higher effectiveness in preventing TB than 6H.[501] In 2024, a child-friendly formulation of rifapentine with dosing guidelines for children became available, making 3HP a preferred regimen in children with access being explored, including in PNG.[290] In late 2024, WHO recommended levofloxacin for TPT in household contacts of MDR-TB index cases following the results of RCTs.[9]

5.4.2 TB Infection prevalence in household contacts and TB transmission

The overall prevalence of TB infection in household contacts was similar to other studies and meta-analyses.[241,495] However, there were some context-specific findings. The prevalence of TB infection in household contacts in Daru was high and greater in MDR/RR-TB contacts across all age groups. The higher prevalence of TB infection in MDR-TB households compared with DS-TB households has been described in a meta-analysis, while noting that a test for infection cannot directly determine drug-resistance of the infecting strain.[502] This may be due to the potential for greater delays in MDR/RR-TB detection and effective treatment, which would increase exposure in households relative to DS-TB; a difference in host or environmental risk factors and/or pathogen factors which may increase the risk of infection/re-infection. A modern Beijing MDR-TB strain with a high number of compensatory resistance-conferring mutations (that do not limit fitness cost) has been identified as the dominant lineage and responsible for the majority of MDR/RR-TB in Daru.[143,148]

The sharp rise in infection prevalence with increasing age from older children to young adults suggests that transmission is occurring outside the household, as social mixing increases with age.[503] This has been observed in other settings, where epidemiological and molecular studies in Peru, South Africa and the Philippines have shown that the majority of non-index cases in households were from community

transmission.[178,239,504,505] The low prevalence of infection in young children (0-4 years) who did not have active TB, was unexpected given the high screening yield in this group. This could reflect lower exposure to TB in these children compared with older household contacts; that is, the index case was not a primary caregiver to an infant or young child. Alternatively, it may have been due to false-negative TST in this age group, although this would be less likely as infants were tested at the same time as older contacts. False negative TST could also have been due to different tuberculin batches or poor-quality assurance (e.g. cold chain rupture). The TST supply was quality-assured, and cold-chain storage was monitored, with no breaches reported in the program.

Notably, the prevalence of TB infection was lower in young child DS-TB contacts tested (1/58), compared with MDR/RR-TB contacts (18/115). The reasons for this difference are speculative, and there are several possibilities. If this was a true finding, it may indicate that there was greater and/or more recent MDR/RR-TB transmission in household contacts in Daru than DS-TB transmission. It should be noted that the case notification rates of DS-TB and MDR/RR-TB have remained relatively stable since 2015 (as described in Chapter 3)**.** Alternatively, there may have been false-negative TST in DS-TB contacts. This could have been due to an operational reason, as MDR/RR-TB contacts and DS-TB contacts were tested at different times in the study. However, this reason would have needed to only apply to children aged 0-4 and not older contacts. It is improbable that quality assurance issues only affected young child DS-TB contacts. Alternatively, the result may have been due to false negatives due differences in testing procedures and quality from different staff administering TST. A more highly trained international nurse performed TST initially in MDR/RR-TB contacts and then trained a PNG nurse to perform TST in DS-TB contacts. It could be plausible that correct TST administration in young children was most operationally challenging for newly trained staff. Finally, there may have been false-positives in the MDR/RR-TB contacts. While BCG vaccination is known to give a false positive TST, it was unlikely to have influences our results. BCG coverage was low across the study period, and when given to infants the effect on a TST reading of ≥10 mm, as used in this study, is minimal and wanes with age.[506]

5.4.3 Observations on household and community transmission

There are some key observations from the epidemiology of household contacts and study findings. The overall bacteriologically confirmed case notification rate in SFD (2014-2022) was 1.14% (includes all active and passive case finding, Chapter 3) and suggests that household contacts in this high-transmission setting may not have

substantially elevated risk compared to the general community. The contact screening yield for all forms of TB of 3.2%, was only modestly higher than the overall TB case notification rate in Daru which has previously been reported at 2.6%,[404] underscoring the high levels of transmission in the community. That 13.2% of contacts had more than one index case, and 3.5% had more than three, demonstrates that transmission dynamics are complex in Daru due to large, multi-generational kinship groups living across multiple dwellings and high levels of population movement.[137,152] Taken altogether, this indicates a high force of infection and evidence of recent transmission in these households. While household contacts are a risk group for TB in Daru, this may just reflect the high risk in the general community. Comparing TB disease and infection prevalence in the general community with household contacts in Daru would be informative in testing this hypothesis. These findings have important implications for prevention strategies in hyper-endemic settings, where community-wide screening for active TB and prevention may be more appropriate than household-focused interventions alone.

5.4.4 Strengths, limitations and programmatic lessons

A strength of this study is its real-world relevance, as contact investigation was conducted under programmatic conditions in a challenging operating environment in Daru. The model of investigation and management was delivered through community health workers, nurses and HEOs, who were embedded in the routine TB program with additional responsibilities for operational research (consent, data collection). This contributed to health systems strengthening as this household contact investigation team has become a part of the routine TB program managed by the WPHA. The demonstration of a functional model of community contact investigation is generalisable to other remote, community-based settings that are resource-limited. The study adhered to the STROBE checklist for observational studies.[507]

While the programmatic tools introduced in this study (e.g. HMTs) were successful in supporting implementation by tracking patients, there were limitations in data collection and management. The ability of the EMRS to meet the needs of the analysis and evaluation was an issue, due to its file structure and need for supervision or expert data manager input. There were gaps in data entry and management that highlighted the unmet need for quality checks and training of local data officers on data entry into the EMRS. Data quality checks could not be performed on site, due to the interruption of the study by the COVID-19 pandemic and demobilisation of staff from Daru. Most importantly, we attempted to link individuals (contacts and cases) across multiple stages of the cascade, multiple screening episodes and health encounters, rather than evaluate

aggregate cascade stages. This was problematic, in part due to the challenges of identifying individuals in the medical records, registers and/or EMRS: there are no unique identification numbers available for use in PNG, variability exists in recall of date of birth and spelling of names, there was no pre-existing electronic health information system in Daru and civil registration coverage in PNG is poor.[508] While active drug safety monitoring systems for TB treatment had been previously established in Daru,[149] adverse event recording and reporting may have underestimated non-serious AEs. Individual TST measurements (in mm) were not systematically recorded; only binary TST status (positive ≥10mm versus negative) was captured. This limits assessment of programmatic quality indicators such as digit preference and prevents full evaluation of whether lower TST positivity in younger age groups reflected true lower infection prevalence or technical challenges with TST placement.

There were several limitations in study interpretation. Overlapping case detection interventions (enhanced diagnostic testing and clinical assessment, systematic screening for TB, household contact investigation) limit attribution of increased case detection to any single component, though this reflects comprehensive TB programme implementation. Non-random missing data for TST results (higher in young children) and nutritional status may bias prevalence estimates and limit assessment of malnutrition as a risk factor. Additionally, malnutrition itself may affect TST interpretation, potentially leading to false-negative results. Molecular epidemiology or genomic sequencing was not available, limiting precision in determining transmission pathways between household members versus community acquisition.

Programmatic challenges and considerations included low levels of health literacy in the community; therefore, community engagement, building trust through community health workers and peers and appropriate education and consent, such as using visual aides were key to addressing this. Dedicated human resources were required for contact investigation (screening and TPT) and operational research. The procurement and uninterrupted supply of quality assured TST was challenging. While aligned with PNG guidelines at the time of the study and consistent with the research protocol approved by the ethics review board and NTP, older contacts (above 5 years) who were TST positive were not offered TPT. Provision of TPT to older contacts was a conditional recommendation in the 2018 WHO guidelines but not widely implemented globally.[283] Finally, the COVID-19 pandemic disrupted the final phases of the study, limiting participant recruitment and post TPT completion follow-up of study participants including late outcomes and/or adverse events. The experience gained in community

engagement and TB household contact investigation was valuable in the vaccination and outbreak response to COVID-19 in Daru.

5.5 Conclusion

These results demonstrate the feasibility of community-based household TB contact investigation and TPT provision for young child contacts in a remote and resource-limited setting. Contact investigation has now been established as a routine programmatic TB activity in Daru and is a priority for the NTP in PNG, to be supplemented with community-based screening in high transmission settings.

The very high prevalence of active TB in household contacts and the general community in Daru requires ongoing intervention, with systematic screening or active case finding and treatment. The high prevalence of TB infection in household contacts, particularly in contacts of MDR/RR-TB index cases, is an important consideration for the expansion of TPT that provides individual benefit and may have a role in reducing community transmission of TB. Since 2020, WHO guidelines have recommended TPT in household contacts of all ages. There are resource and programmatic implications if PNG were to implement the newer WHO recommendations for TPT in older contacts – including consideration of the appropriateness of TST and identification of an appropriate regimen in a high-MDR-TB setting, where concordance to index cases may be low. Levofloxacin has been shown to reduce the incidence of TB among MDR-TB/RR contacts and while this effect is very likely to be seen in DS-TB contacts, it has not been specifically evaluated.

However, this study also revealed significant challenges and limitations of household-based approaches in Daru's unique transmission context. The finding that 13.2% of contacts had multiple index cases, the complex kinship networks identified in Chapter 4, and the high community transmission rates documented in Chapter 3 suggest that household contact investigation, while feasible and beneficial, may be insufficient as a standalone screening and prevention strategy in this setting.

This implementation research study on contact investigation has informed the subsequent phase of the response to TB in Daru, through the expansion to a community-wide approach to detect, treat and prevent active TB and TBI, using households as the unit of intervention, which commenced in 2023 (Chapter 7). The programmatic lessons learned from this implementation, along with the challenges encountered and potential solutions, are analysed in detail in Chapter 6. Community-based approaches to detecting

and preventing TB are essential components of approaches to end TB, promote equity and access to care and promote more resilient health systems and services in resource-limited settings.

Chapter 6: Contact investigation in a high-transmission MDR-TB setting in Papua New Guinea 2017 - 2022: progress, challenges and future directions

This chapter presents a critical reflection and analytic summary of programmatic lessons learned from community-based household contact investigation in Daru, Papua New Guinea from 2017 to 2022. Building on the implementation research study presented in Chapter 5, this work was developed with the PNG-based implementation team, reflecting our collective experience. The lessons captured in this chapter formed the rationale for developing the comprehensive community-wide approach detailed in the SWEEP-TB protocol (Chapter 7). This chapter has been published in a peer-reviewed journal (Appendix 6.1).

6.1 Introduction

Tuberculosis (TB) is the leading infectious cause of morbidity and mortality in Papua New Guinea (PNG).[91,407] The emergence and increasing transmission of multidrug-resistant TB (MDR-TB) is a major challenge.[408] On Daru Island in the South Fly District of Western Province, PNG, there is an unprecedented MDR-TB outbreak with a TB notification rate of 2,021 per 100,000 for all TB and 594 per 100,000 for MDR/RR-TB (rifampicin-resistant) in 2015.[147,404] In 2014, the PNG National Department of Health and Western Provincial Health Authority (WPHA) initiated an emergency response to MDR-TB, which has resulted in the stabilisation of TB notifications, improved treatment outcomes and a reduction in TB-related mortality.[157,404] A description of the geographical, social and demographic context in Daru, which is located in the transboundary region between PNG and the Australian Torres Strait, has been detailed elsewhere.[137,152]

A comprehensive community-based model of care for TB was established through the introduction of evidence-based practice, with significantly improved outcomes and introduction of novel tools including bedaquiline-containing treatment regimens.[149,404,496] Community engagement and patient-centred support services have been central to delivery of care.[150] An electronic patient-level medical record system (EMRS - Bahmni, Thoughtworks) was implemented in 2016 to support quality patient care, program monitoring and operational research.[149,404] The investigation (also referred to as screening) and management of household contacts of people with TB commenced in 2016. TB preventive treatment (TPT) for well young child (<5 years) contacts of drug-

susceptible (DS) TB index cases was introduced in 2017 and extended to those of MDR/RR-TB index cases in 2019.[397]

In Daru, as in many other high-transmission and resource-limited settings, best practice strategies and tools for TB and MDR-TB, as defined by the World Health Organisation (WHO), are often under-utilised or not prioritised and slow to translate into national guidelines.[18] Active case finding through contact investigation and TPT for eligible at-risk contacts has been programmatic priority for the WPHA TB program since 2016 as part of a comprehensive approach to reduce TB and MDR-TB transmission (WPHA Annual Implementation Plans). The National TB program (NTP), which provides normative guidance and guidelines for the programmatic management of TB to provincial health authorities in PNG, did not have specific guidelines for contact investigation and TPT and referred to WHO guidelines.[159,167,196,283] However, application of WHO guidelines to high transmission MDR-TB settings presents additional challenges that require specific considerations and novel approaches. Table 6.1 summarises the approach, challenges and solutions for contact investigation in Daru, PNG from 2017 to 2023.

6.2 Approach to household contact investigation (2017 – 2022)

In Daru, a dedicated public health TB Team consisting of a health extension officer (an auxiliary medical officer), nursing officers, community health workers and health promoters conducted household contact investigation for all newly detected bacteriologically confirmed pulmonary or extrapulmonary TB under the supervision of a medical officer, following local standard operating procedures. Contact investigation and management was conducted in a community-based model of care, with engagement and screening at households or locations within the community in Daru, with clinical review and TPT for young child contacts provided at decentralised treatment sites (community TPT clinics) that were established for active TB treatment and care. Following verbal consent by index cases or their guardian and the household head, contact investigation occurred with households as the unit of intervention. Education was provided by trained health promoters to household contacts, who were defined as any person who lived in the same house as the index case within three months prior to diagnosis, including spending time during the day. Contacts were screened for symptoms or signs of active tuberculosis and for malnutrition. Chest radiography (CXR) was not used for screening. A positive screen was defined as one of cough, fever or night sweats for more than two weeks, reported weight loss, moderate to severe malnutrition on screening or signs of extrapulmonary TB. Young children were screened for malnutrition using mid upper arm

circumference and weight for height for those under 6 months. Moderate to severe malnutrition was managed according to local guidance for child nutrition and includes empiric treatment for soil transmitted helminths. Contacts who screened positive were referred to the TB diagnostic clinic at the Daru Provincial Hospital (DPH) for further investigation of active TB. Asymptomatic young child contacts (<5 years) were referred to the TPT clinic.

6.2.1 Detecting active TB in contacts

TB detection with treatment of disease is a critical role of contact investigation along with determining eligibility for TPT. At the DPH TB diagnostic clinic, household contacts with a positive community TB-related symptoms are referred for further investigation including CXR and appropriate specimens such as sputum or lymph node aspirate for Xpert Ultra as per PNG and WHO guidelines.[37] If RR-TB is detected, a specimen is sent to the national laboratory for culture and drug-susceptibility testing and molecular assays for early diagnosis of fluoroquinolone-resistance. Gastric aspirate and/or stool samples for Xpert Ultra are taken from symptomatic child contacts unable to expectorate sputum. Asymptomatic contacts (screen negative) are not routinely referred for investigation, including asymptomatic young child contacts, who are eligible for TPT.

6.2.2 TB Preventive Treatment

The provision of TPT to household contacts has been long recommended in WHO guidelines, but implementation in resource-constrained settings remains limited.[116,122,283,284,509] TPT should be routinely offered to well (asymptomatic) young child (<5 years) household contacts of people with confirmed or presumptive pulmonary DS-TB.[116,159] To be eligible for TPT, young child contacts only require symptom screening to exclude active TB and do not require a test for TB infection, i.e. tuberculin skin test (TST) is not required for TPT eligibility.[159,287] Guidelines for older (≥5 years) household contacts have evolved over time, with WHO making a conditional recommendation in 2018 to consider TPT following testing for TB infection.[283] The protective efficacy of TPT is well established[52] and the recently recommended shorter regimens (one to four months duration) are associated with high rates of completion and very few adverse events.[159]

The program in Daru was the first in PNG to systematically introduce a community-based model of TPT in 2016 using 6 months of daily isoniazid (6H) for young child contacts. A TPT regimen of 3 months of daily rifampicin and isoniazid (3HR), recommended by WHO in 2018[283], has been associated with high uptake, completion and safety in young child

contacts under programmatic conditions in resource-limited settings.[499] The availability in PNG of dispersible, child-friendly combined formulations for active TB since 2016,[486] led to the successful implementation of 3HR for young child contacts of DS-TB in Daru from 2019.

In Daru, 32% of incident bacteriologically confirmed TB is MDR/RR-TB (chapter 3).[404] TPT as 3HR or 6H may not be protective for child contacts of MDR-TB and is not recommended in this context.[159] Furthermore, known exposure to DS-TB does not necessarily determine that infection is limited to a drug-susceptible strain only.[348,510] The optimal TPT regimen following infection with MDR-TB is unknown. A regimen that includes daily levofloxacin for at least six months (6Lfx) is widely used. Observational evidence from a number of settings suggests that a fluoroquinolone-based TPT regimen in MDR-TB contacts with evidence of TB infection (TBI) can substantially reduce the risk of developing MDR-TB, and with no significant safety concerns.[123,124,444,489,511] This protective benefit has now been confirmed by two RCTs of 6Lfx for MDR-TB child and adult contacts, and led to updated WHO recommendations and guidelines in 2024.[9,490,500]

The use of TPT in MDR-TB contacts requires an assessment of potential benefit versus risk, and benefit is greatest in contacts with infection.[52] In 2019, tuberculin skin test (TST) was introduced in Daru to determine eligibility for 6Lfx as TPT for young child contacts of index cases with bacteriologically confirmed MDR-TB (without fluoroquinolone resistance) as part of a pilot project (chapter 5). This age group was selected as being high risk for disease due to care-giving relationships and high likelihood that exposure occurred in the household of the index case. A similar model of implementation was used as for 3HR for young child contacts of DS-TB, with the addition of TST. An operational research protocol with ethical approval was obtained and following informed consent, young child contacts with a positive TST and no evidence of disease on symptom screening and clinical examination were offered 6Lfx. To date, an effective model of care for household contact investigation has been established with high uptake and completion (Chapter 5).

6.2.3 Community Engagement and Patient Education

Community engagement and education is critical to support contact investigation, and especially to support TPT uptake and adherence given that this requires giving medication daily for months to a child or adolescent who is well. In Daru, several approaches are utilised to deliver education to people on treatment, their families and

the wider community. An international community-based organisation has been providing TB health promotion and social mobilisation activities since 2011, focussing on enhancing detection and treatment support for active TB.[157] A peer counselling model was introduced in 2017 involving People who have been Affected by, Living with or having Survived TB, known as PALS, who are trained and mentored to provide education and counselling support.[150] The counselling program initially focused on support for people on treatment for active TB and expanded in 2018 to include families of children on TPT.

Locally tailored education materials including visual tools were developed, tested with community, and guides created for standard counselling sessions scheduled at key points of treatment. A child-friendly space with activities was initiated at the TPT follow-up clinic. Counselling and education are provided in the family's preferred language where possible. Due to the limited health literacy and linguistic diversity (>3 languages) of the people South Fly District, visual tools and aides have been important. The term "sleeping TB" was used to explain the concepts of TBI. Community education and health promotion campaigns to increase understanding of "sleeping TB" and TPT were conducted including promotion from the town mayor and local leaders, public education sessions at churches, schools, sports events, community locations and local radio. The above measures have contributed to high rates of adherence and TPT completion.

6.2.4 Program monitoring and data systems

Monitoring and evaluation of contact investigation programs are essential. However, comprehensive guidance does not exist regarding tools, data definitions or processes for programs to implement contextually adapted solutions. The WHO has defined minimum data and indicator definitions for TPT, and the Zero TB Initiative has outlined a comprehensive set of indicators for the search-treat-prevent approach.[170,512] The EMRS in Daru was adapted to include modules for contact investigation and TPT in 2018. A household mapping tool that documents investigation of all close contacts of an index case is used as previously described.[397] The public health team records patient data using paper-based records. A data entry team subsequently enters this data into the EMRS. Contact investigation and management is monitored by the TB program using a cascade-of-care framework for TB detection and prevention. The EMRS enables reporting of an individual-level cascade, rather than aggregate. Resources required to support the EMRS, including information technology expertise, programming skills and data entry capacity, are provided through partner support. Despite challenges,

implementation has been successful, with the data system monitoring TPT uptake and outcomes.

6.3 Implementation challenges and considerations

Operational challenges include a chronic shortage of health care workers, interruption of CXR services, laboratory reagents and power and internet outages. The availability of international partner support has been critical to the TB program in Daru since 2011. Adopting a community-based model with mobile teams and task-shifting from medical and para-medical staff to nurses and community-health workers with training and technical support from partners has helped to address human resource issues. The emergency phase of the COVID-19 pandemic had a major impact on the delivery of TB services. From March 2020 until April 2022, contact investigation was suspended initially due to public health restrictions and infection risks and subsequently health workforce shortages (Chapter 3). Programmatic focus over this period was active TB treatment and care with case-finding limited to facility-based only (passive). Household contact investigation restarted in April 2022.

Daru, and South Fly District have significant particular challenges in the social determinants of health which contribute to increased risk of TB transmission, with one of the highest measures of household poverty in the region, low levels of health literacy, overcrowding, food insecurity and low access to health services due to service availability, remoteness and lack of trust.[137,152] The TB program has had a concerted focus on community engagement, health promotion and patient-centred services. A major challenge has been household engagement and entry into communities. This has been successfully addressed through the engagement of community leaders, household heads and community education. This patient and family-centred approach have built trust with the community over time, as has the engagement of people who have survived TB as peer counsellors in the program.[150] Timely referrals for eligible TPT candidates for pre-initiation counselling by peer counsellors also reduced delays in engagement in TPT care. In the early implementation of TPT for young children, adherence issues were noted prompting an exploration and development of solutions for these contributing factors such as stigma and consent, through peer counsellors (Chapter 4).

A Community Advisory Group, self-named TB Nanito Kopia Kodu (the Voice to Kill TB Forever) was formed from community consultations in late 2019 with members representing key stakeholder groups (e.g. churches, schools, businesses, key

populations). The group's primary focus is providing community input and co-design for TB public health activities, including the development of community education materials and models to reach key populations such as adolescents and students, working adults (not present at home), prisoners, people with disabilities and the elderly. Accordingly, a comprehensive community education campaign has been developed with a participatory approach involving training of representatives from key populations.

Re-identification of individuals during multiple episodes across the screening and prevention cascades of care has been a particular challenge due to poor civil registration coverage.[513] In PNG, people may give different names, age and residence from visit to visit with addresses not specific enough. Paper-based recording at multiple points of care also contributes to the problem by making it difficult to check a patient's details against existing information. The linkage of contacts to multiple index cases needs to be reconciled for reporting. This is currently addressed through local health worker and community knowledge of households and engagement via peer counsellors. Biometric systems have been proposed as a solution for patient identification, but cost, complexity and acceptability are barriers to implementing them. An immediate solution is patient-held records, such as health books or a card that can be issued and used to identify patients. However, these may get lost or not brought to patient visits. A potential solution for re-identification at low cost that supplements patient-held records with a memorisable unique identifier consisting of three common objects, represented with images was designed and piloted. Even partial recall of this identifier can aid re-identification.

The primary challenge in Daru is the application of the household as the unit of intervention for contact investigation and to deliver post-exposure management including detection of active TB and TPT. This is both from an implementation perspective and the fact that households may not be the optimal unit of intervention for timely detection of active TB and identifying those at risk of recent exposure for TPT.[178,514] The socio-cultural context in Daru, as elsewhere in PNG, involves large multi-generational family structures based on kinship. However, there are some unique features with significant overcrowding in settlements and frequent travel between mainland villages and Daru Island, often for extended periods of time. This results in large "households" with complex family structures and population movement. Therefore, the operational household contact definition used is broad and includes those who have spent more than one night in the household in the past 3 months, including the extended family network.

Several lines of evidence, when taken together suggest that Daru is that most transmission is likely occurring outside the household, as noted even in children in other high-incidence settings.[178] The likelihood of exposure and infection occurring outside of the household increases with age (Chapter 5). Adolescence is a peak age for close and casual social contact and so in a highly endemic setting such as Daru, the majority of the population may be infected by adulthood. [179] TST testing in MDR-TB household contacts in Daru has demonstrated a high prevalence of infection similar to reported elsewhere.[342] The majority of TB and MDR-TB notifications are in older adolescents and young adults, with around 70% of TB notified in those 15-34 years.[404] Furthermore, with large household sizes and a very mobile population, an individual can be exposed to multiple index cases concurrently, including DS and MDR-TB. Therefore, consideration of alternative approaches in Daru to household contact management are warranted for the goals of preventing TB in those at risk and reducing community transmission.

6.4 Future directions – moving beyond household contact investigation

Until recently in high TB transmission settings, recommendations for TPT have been limited to specific high-risk groups for disease such as young child contacts and people living with HIV.[159] While important in reducing tuberculosis-related morbidity and mortality in these groups, the impact of TPT on community transmission by preventing new cases is small, likely negligible for young child contacts.[178,515] Therefore, a community-wide strategy has been considered in the design of an enhanced public health intervention and model of care that aims to increase TB detection and treatment while providing TPT to a broader population to reduce transmission in addition to TB morbidity and mortality.[128,129] Figure 6.1 outlines our considerations for a comprehensive detect-treat-prevent strategy in a high TB transmission setting by age that were formulated in 2021.

First, programmatic scaling-up of contact investigation that includes older children, adolescents and young adults in the community is planned. The 2020 WHO recommendations include a wider age range of TPT options for HIV-uninfected contacts.[159] We therefore propose community-wide TST testing for Daru residents aged 5-34 years irrespective of known household exposure, with TPT provided to those with infection and no evidence of active TB, as part of a comprehensive approach to complement active case-finding. The model of community engagement and implementation described above will be applied and the household will be the unit of intervention. The application of a community-wide systematic screening for case

detection aligns with recent (2021) WHO recommendations for settings with a TB prevalence of 0.5% such as Daru, and is based on new evidence of public health benefit following annual community screening in Viet Nam.[167] The decision to provide TPT for 5-34 years with infection is based on the following considerations: high-risk age group for active TB; high risk age group for transmission in the community; and lower risk of isoniazid-related toxicity due to TPT compared 35 years and older.

Second, in high transmission MDR-TB settings, consideration of a TPT regimen for older children, adolescents and adults that considers the possibility of infection with an MDR-TB strain irrespective of the index case is needed. A novel option is a combination TPT regimen of 6 months of daily isoniazid and levofloxacin (6HLfx) for 5–34 year-olds with evidence of infection and no active TB. This TPT regimen was chosen to effectively treat infection with either DS or MDR-TB as a positive TST cannot determine drug susceptibility of the TB infection. While exposure to both is common, the majority (>80%) of TB in Daru is DS-TB. Isoniazid or rifampicin may not effectively treat infection with an MDR-TB strain. While it is plausible that levofloxacin alone may be effective in people who have DS-TB infection, there is no evidence of effectiveness outside MDR-TB exposure (household contacts).[490,500] There is circumstantial evidence that isoniazid may also be effective in the treatment of MDR infection.[348] Rifapentine is currently not available in PNG and a three-drug regimen may have additional adverse effects over two. Therefore, isoniazid is included in the proposed regimen. Young child (<5 years) contacts can be managed as per the strain of the index case. The optimal approach for management of fluoroquinolone-resistant TB infection is uncertain and should be individualised.

Third, it is critical to exclude active disease especially in adolescents and adults. An optimal age-related contact management algorithm is required to mitigate the risk – individual and public health – of generating resistance including to fluoroquinolones. This risk needs to be negligible, similar to isoniazid and rifampicin.[352,353] In addition to symptom screening, the inclusion of CXR and sputum Xpert Ultra in the algorithm will provide high sensitivity for detection. The optimal age-related use of chest-radiography in asymptomatic, HIV-uninfected people aged 5–34 years to rule out active TB before TPT is unclear.[170] WHO guidelines recommend that asymptomatic young child contacts (<5 years) or PLHIV do not require CXR before TPT initiation. It is likely that the same approach could be applied to all well children (<10 years) with infection without risk of not detecting sub-clinical disease.[516] This is the approach that is being considered in Daru as it would reduce the requirement for clinical assessments in children <10 years.

In addition to a negative symptom screen, CXR will be routinely included in screening adolescents and adults (≥10 years), as it is important to exclude active TB with a sensitive algorithm prior to TPT initiation.[518] Computer-aided detection of CXR is recommended for TB screening in people ≥15 and this will also be used for screening young adolescents (10-14 years). This is because adolescents with TB commonly present with adult-type disease such as with cavitation, most critical to rule-out before initiating TPT.

The significant health individual and health system burden of ongoing MDR-TB transmission is a compelling argument for the potential benefit of the community-wide approach to detect, treat and prevent DS and MDR-TB and likely outweighs potential individual treatment risks with 6HLfx.[18,518] Operational mixed-methods research will evaluate the impact, acceptability, feasibility and cost-effectiveness. The intervention will build on the local leadership, programmatic experience and platform of innovation that has been established in Daru. Ongoing engagement and placing the affected community at the centre of the response remains critical to success and towards ending tuberculosis in high-transmission settings.

Table 6.1 Contact investigation and management – current approach, challenges and solutions in Daru, PNG 2017 - 2022

Program Area	Approach to date	Challenges and considerations	Solutions and future directions
Model of contact investigation and management	Community-based (decentralised clinics) Non-specialist public health team Health promoters and education Integrated screening for malnutrition and treatment for helminths in young children (<5 years) Standard monthly follow up, including education and counselling if required	Human resource shortage Operational interruptions to CXR, laboratory and internet COVID-19 impacts led to suspension of contact investigation Large multigenerational households and contact networks (kinship, visitors) – definition of household	Community-wide screening: detect, treat, prevent approach with evaluation Task-shifting to nurses and community health workers Technical partner implementation support Households as unit of intervention
Detecting active TB	Referral to hospital, dedicated TB diagnostic service Gastric aspirate, lymph node aspirates and stool samples performed for mWRD e.g. Xpert Ultra CXR	Excluding active TB in children and adolescents Optimal use of CXR, especially in 5-14 years – as abnormalities require follow-up CXR screen with CAD not validated for children (<15 years)	Excluding active TB in children and adolescents with sputum and/or extrapulmonary samples for mWRD and CXR Optimal use of CXR screening, consider in all >10 years with CAD
TB Preventive Treatment (TPT)	TPT to young child contacts(and people living with HIV) Shorter TPT regimen: 3HR for DS-TB exposure (Xpert MTB/RIF negative) 6Lfx if evidence of infection (TST positive) for MDR/RR-TB exposure	Household exposure may not correlate with resistance of infecting strain as transmission occurring outside the household and multiple index cases Who to test for TB infection Optimal TPT for a high MDR-TB setting – regimen, age-related risks Fluoroquinolone resistant exposure	TPT for <5 years according to household exposure TST to detect infection for TPT in 5-34 years TPT for TST positive in 5-34 years with novel combination regimen, 6HLfx to cover DS- and/or MDR/RR-TB Individualised approach to fluroquinolone resistant TB exposure
Community education & patient education and support	Community education and health promotion campaign to explain “sleeping TB” (TB infection) prior to TPT service initiation Peer counselling model. With family-based care Visual tools and aides (education games) Child-friendly space in TPT clinic	TPT for the well Structural barriers – poverty, low health literacy, overcrowding, food insecurity, Stigma and trust Mobile population	Community advisory group to co-design public health activities and education materials Engagement of priority populations Continue peer-led model Person-centred care
Program monitoring and data systems	Paper-based household mapping tools for contact investigation EMRS for data entry, management, reporting and analysis Cascade of care indicator set (individual or longitudinal)	Comprehensive guidance on tools, definitions and processes for contact screening and management not available Resources required to support EMRS The need for re-identification across multiple health interactions for care No government or health ID system	Continue EMRS and cascade reporting Unique identifiers: health book with ID and verbal ID. Biometrics not feasible. Cascades of care for quality improvement

CXR: chest X-ray; mWRD: molecular WHO-recommended rapid diagnostic test; CAD: computer-aided detection; TST: tuberculin skin test; TPT: tuberculosis preventive treatment; H: isoniazid; HR: rifampicin and isoniazid; Lfx: levofloxacin; HLfx: isoniazid and levofloxacin; DS: drug-susceptible; EMRS: electronic medical record system; ID: identification

Figure 6.1 Considerations for a comprehensive detect-treat-prevent strategy in a high MDR-TB transmission setting by age

	< 5 years	**5-14 years**	**15-34 years**	**35-54 years**	**≥55 years**
Potential impact on transmission	Minimal +/-	+	+++	++	+
Symptom screen[1]	For all ages				
CXR if symptom screen negative	Not recommended	Uncertain	Recommended		
Test (sputum) for active TB and resistance with mWRD	For symptomatic and abnormal CXR		For all – symptomatic, CXR abnormal and consider in asymptomatic if able to provide sputum		
Test for infection for TPT initiation	Not required	Recommended			
TPT indicated	If TB-exposed and asymptomatic	If evidence of TB infection		Uncertain	
TPT regimen	3HR if DS-TB exposure 6Lfx if MDR/RR-TB exposure	Consider combination regimen in high MDR setting: 6HLfx			
TPT safety	+++	+++	++	+	+

1A positive screen was defined as one of cough, fever or night sweats for more than 2 weeks, reported weight loss, moderate to severe malnutrition on screening or signs of extrapulmonary TB

+++: high; ++: moderate; +: low; +/-: uncertain

CXR: chest X-ray; mWRD: molecular WHO-recommended rapid diagnostic test; TPT: tuberculosis preventive treatment; HR: rifampicin and isoniazid; Lfx: levofloxacin; HLfx: isoniazid and levofloxacin; DS-TB: drug-susceptible tuberculosis; MDR/RR-TB: multidrug-resistant/rifampicin-resistant tuberculosis

Chapter 7: Systematic Community-Wide Engagement & Elimination Project for TB in Daru, Western Province, Papua New Guinea: SWEEP-TB Daru Protocol

This chapter is a research protocol that was developed as part of this thesis and initially submitted for ethical review in Papua New Guinea in March 2021, revised, resubmitted in December 2021 (version 1.3) and approved in April 2022 (PNG Medical Research Advisory Committee). The protocol was submitted for ethical review in Australian in October 2022 and approved in November 2022 (Alfred Health Ethics Committee). This chapter content reflects an amendment to the protocol was made in October 2023 (SWEEP-TB version 1.4).

7.1 Background & Rationale

Tuberculosis (TB) is the major infectious cause of morbidity and mortality in Papua New Guinea (PNG).[91,407] The emergence and increasing transmission of multidrug/rifampicin-resistant TB (MDR/RR-TB) is a major challenge.[143,144,408] On Daru Island in the South Fly District of Western Province, PNG, there is an unprecedented MDR-TB[4] outbreak with severe consequences for the health of the population, health services and continued risk of epidemic spread to elsewhere in PNG.[147,148,404] In 2014, the PNG National Department of Health and Western Provincial Health Office (now Provincial Health Authority, PHA) convened an emergency response to MDR-TB in Western Province with funding support from the Australian government and mobilisation of international partners, including Burnet Institute and World Vision.[147,404] This response has resulted in a plateauing of incidence (case notifications) and a reduction in TB-related mortality.[404,520] A high-quality patient-centred model of care has been established through introduction of evidence-based practice and novel tools including bedaquiline-containing treatment regimens (Chapter 3).[149,150] Since 2017, the screening and management of household contacts of TB cases has been successfully introduced, which has included TB preventive treatment (TPT) for well young child (i.e. <5 years) contacts of TB cases, both those with drug-susceptible (DS) and MDR-TB (Chapter 5).[397]

[4] In this protocol, MDR-TB will refer to MDR/RR-TB, as Xpert Ultra is used as the front-line test for TB detection

A state-of the art electronic health information system was established on Daru in 2017 to enable program evaluation and research.

This implementation research is embedded in a public health intervention and aims to substantially reduce TB incidence (case notification) in the population of Daru by the implementation of a comprehensive community-wide strategy that combines enhanced case detection, effective treatment and novel strategies for prevention, including preventive therapy for MDR-TB. The research project is entitled, Systematic Community-Wide Engagement & Elimination Project for TB in Daru (SWEEP-TB Daru) or Yumi Bung Wantaim Na Rausim TB Long Daru. This proposed study is objective 1.4 of the South Fly District TB Annual Implementation Plan (2019-2022) and will be conducted under the stewardship of the WPHA. The implementation of SWEEP-TB will be as per the routine WPHA TB program which is through the Director of Public Health to the WPHA Chief Executive Officer. Significant community engagement, consultation and co-design in Daru have been undertaken specifically for this proposal in collaboration with World Vision PNG.[94] This started with community consultation workshops in November and December 2019 from which a community advisory group was established to consult, engage, and seek feedback from the people living in Daru. This group includes people who have survived TB, church and business leaders and youth representatives. There is strong local political support including from the Daru mayor and ward members.

The research will be implemented by the WPHA and the Burnet Institute in collaboration with the National TB Program (NTP), the University of Papua New Guinea (UPNG) and the PNG Institute of Medical Research (PNG IMR). Since 2014, the Burnet Institute has supported the Western province MDR-TB outbreak response and PNG TB response through technical assistance and research capacity building initiatives. Burnet, PNGIMR, UPNG and NTP have established a TB research partnership, that includes conducting the first Structured Operational Research Training course for TB in PNG (SORT-IT) from 2017-19,[158] facilitating the establishment of a TB research advisory committee under the leadership of the NTP and supporting PhD research and laboratory training to investigate the molecular epidemiology of MDR-TB in PNG.[143] Through this research capacity building program, the WPHA TB program has published 6 research papers with PNG first authors.[149,397,404,432,521,522] Throughout the implementation of SWEEP-TB, there are plans to further strengthen PNG TB research capacity.

7.2 Rationale

There are an estimated 10 million cases each year globally due to TB, causing 1.3 million deaths in 2022.[91] TB elimination is a global health goal but approaches currently used in high TB burden countries will only result in a decline in TB incidence by 1.5% per year.[20] A radically different approach is needed, and the combined implementation of currently available tools has huge potential. A recent trial in Viet Nam reported a 44% reduction in the prevalence of bacteriologically confirmed pulmonary TB through annual community-wide active case finding using Xpert MTB/RIF and treatment over only a three-year period.[205] This study demonstrated a proof of concept that systematic screening for active TB can have a large impact in a short time period, by reducing the number of infectious people with TB, including sub-clinical TB, in a community.[100] Similar impact in TB elimination was seen in active case finding campaigns with chest radiography (CXR) in HICs in the 1950s to 1970s. [36,174] However, WHO guidelines did not recommend active case finding for TB at scale in high TB transmission settings, which are LMICs, and there were concerns over cost, feasibility and cost-effectiveness. In 2021, WHO guidelines recommended that systematic screening for TB disease may be conducted among the general population in areas with an estimated TB prevalence of 0.5% or higher, which would include Daru.[167]

The WHO End TB strategy states that TB elimination at a national or sub-national level cannot be achieved without a comprehensive strategy to address TB infection (TBI), particularly in settings with high rates of transmission.[20] Seminal studies in the pre-MDR-TB era and modelling suggest that combining the detection and treatment of TBI with the detection and treatment of active TB results in a greater, more rapid and sustained reduction of TB incidence than active case detection and treatment alone.[128,129,262,268] Treating TBI or TPT has been recommended by WHO for eligible contacts and other risk groups such as people living with HIV, based on individual clinical benefit (risk reduction of developing active TB).[159] Systematic testing and treatment for TBI is not generally recommended, with the 2020 WHO guidelines for TPT recommending it may be considered for prisoners, health workers, immigrants from countries with a higher TB burden, homeless people and people who use drugs.[159]

Key knowledge and implementation gaps remain in the consideration of community-wide approaches to TPT. First, which populations and individuals to target for treatment of TBI. Second, the role of testing for TBI, noting that there is no gold standard test for direct identification of *M. tuberculosis* infection in humans. The current tests – tuberculin

skin tests (TST) and interferon gamma release assays (IGRA) detect persistent immune response to stimulation by *M. tuberculosis* antigens. Third, the acceptability and feasibility (including tolerability) of current regimens provided to individuals who are well, and at scale. Finally, the application of TBI testing and treatment to high burden MDR-TB settings presents a particular challenge as there are no WHO recommendations for specific regimens to treat TBI in people exposed to or potentially exposed to MDR-TB, with an individualised risk assessment recommended in household contacts of people with MDR-TB.[159] Bacillus Calmette-Guérin (BCG) is the only registered and available vaccine for TB, and it has been long recommended as a birth dose vaccination in TB endemic countries. BCG has effectiveness in preventing infection and disease, mainly severe forms of TB in children.[522] More recently, BCG re-vaccination in adolescents has shown effectiveness against sustained IGRA conversion in adolescents.[112] Due to its limited effectiveness against infection in adults, BCG does not have a durable population effect in reducing transmission.

It is imperative for the local community in South Fly, Western Province and more broadly for PNG that the MDR-TB outbreak is not just contained but eliminated. In Daru, as in many other high-transmission and resource-limited settings, available strategies and tools for TB and MDR-TB are under-utilised.[18] A comprehensive approach that seeks to detect, treat and prevent all forms of TB has not been implemented or evaluated, and yet evidence of effective interventions is urgently required from such settings. For a major impact on transmission and disease burden in Daru, we propose that in addition to systematic screening for active TB and treatment, TPT will need to be extended beyond a focus on young child contacts (<5 years) to include adolescents and young adults in the community. Adolescents and young adults (10-34 years) have a very high incidence of TB in Daru – as in PNG overall - and the majority of the most infectious (i.e., bacteriologically confirmed pulmonary) TB cases, including MDR-TB cases, occur in this age group (Chapter 3).

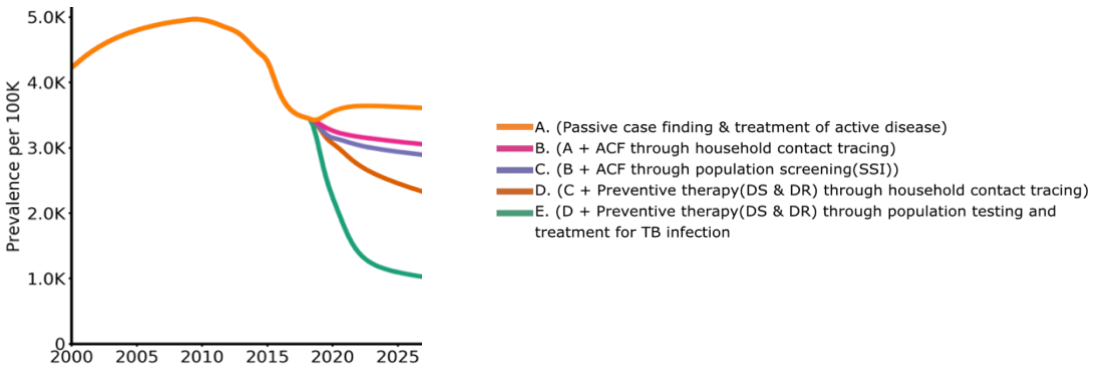
We propose to undertake research that evaluates the implementation of a comprehensive strategy for Daru residents that combines the detection and treatment of active disease and infection. Aligned with pillar 3 of the End TB strategy, we will improve utilisation of “old” or established tools – BCG vaccine, TST, chest radiography (CXR) and TPT – and also “new” or recently introduced tools – Xpert Ultra, mobile digital CXR with artificial intelligence (computer-aided detection for TB, CAD4TB), plus TPT for MDR-TB. Active TB will be treated according to drug-resistance pattern. Young children (<5 years) will be offered TPT only they have been exposed as a close contact and based

on the susceptibility pattern of their index case, while adolescents and young adults (5-34 years) with infection but not disease, i.e. TBI, will be offered TPT for infection with both DS and MDR-TB strains. High rates of TPT uptake, adherence and treatment completion will be critical for effectiveness of the intervention. Those without evidence of TB disease or infection will be offered BCG if not previously vaccinated.

The majority of MDR-TB transmission on Daru Island is occurring outside of households and in adolescents and young adults with 68% of TB and MDR-TB case notifications in those <35 years (Chapter 3). Although there is frequent population movement between villages in the surrounding South and Middle Fly districts, 70% of notified DR-TB cases identify as residents of Daru (Chapter 3). Household contacts of confirmed MDR-TB cases on Daru have a high prevalence of TBI (Chapter 5, Figure 5.2). The TBI prevalence increases sharply in adolescence suggesting transmission outside the household when social interactions increase. Our pilot study of household contact screening in Daru has highlighted population mixing dynamics, i.e. contacts often have multiple index cases, including DS and MDR-TB (Chapter 5). While additional data of TBI prevalence in Daru residents who are not known household contacts are required, a comprehensive intervention to detect, treat and prevent TB in Daru residents with a focus on adolescents and young adults would likely have a major impact on the DR-TB outbreak.

Further, we have performed transmission modelling and cost-analysis of potential intervention scenarios in Daru, using the Optima TB model (Figure 7.1**)** with full details in Appendix 7.1). Treating individuals with TBI using a population-based test and treatment approach (scenario E) offers the greatest and most rapid reduction in TB prevalence which is sustained. This comprehensive approach is more cost-effective by around 40% over the current response (scenario C).

Figure 7.1 Transmission modelling of five response scenarios (A to E) on TB prevalence in Daru, 2018 – 2025



The severe consequences of the very high levels of TB and MDR-TB transmission in Daru required an immediate effective response while awaiting scientific advances such as new rapid diagnostics for infection and disease and evidence of efficacy of TPT in MDR-TB. At the time of protocol development in 2020, there were two ongoing RCTs of levofloxacin for 6 months as PT in MDR-TB contacts which subsequently demonstrated effectiveness in preventing TB in 2024.[490,500] Observational evidence from over 600 MDR-TB contacts suggested that treatment of infection with a fluoroquinolone-based regimen can substantially reduce the risk of developing MDR TB.[123,124] An MDR-TB outbreak in Micronesia was successfully addressed using contact management and TPT for MDR-TB.[444]

A novel combination TPT regimen of 6 months of daily isoniazid and levofloxacin (6HLfx) for TST-positive individuals in Daru without active TB under the age of 35 years is proposed for this study as a key intervention in the comprehensive package. The rationale for 6HLfx is that it aims to treat infection with either DS or MDR TB - exposure to both is common in Daru and a positive test for infection cannot distinguish between infection with a DS or MDR TB strain, or both. Isoniazid or rifampicin will not be effective as treatment of infection with an MDR strain. While it is plausible that levofloxacin alone may also treat drug susceptible TBI, there is insufficient evidence currently available of its effectiveness. Therefore, isoniazid in the proposed combination regimen is primarily aimed at treating DS TBI. However, there is circumstantial evidence that isoniazid may also prevent MDR-TB disease and be effective in the treatment of drug-resistant infections.[348]

The enormous individual and health system consequences of MDR-TB make a compelling argument for the potential benefit of TPT to reduce the incidence of MDR-TB and its cost-effectiveness.[18,518] However, it is also important to consider the potential risks of a novel intervention. There is extensive clinical experience in using prolonged levofloxacin demonstrating safety, including for MDR-TB treatment.[523] There are also now unpublished safety data to add to the published observational data that specifically relates to the use of levofloxacin as TPT in more than 2,000 children and adults who are MDR-TB contacts.[124,524,525] This includes safety data reported from the above mentioned ongoing randomised trials - one involving mainly adults and adolescents in Viet Nam (VQUIN MDR trial) and the other focusing on young child contacts in South Africa (TB-CHAMP).[490,500] In addition to drug-related safety, there must be negligible risk for the individual and the community of the emergence of fluoroquinolone-resistant active TB. As yet, there are no data or evidence of potential risk associated with the specific use of a fluoroquinolone such as levofloxacin, though there is evidence that the use of isoniazid alone or a rifamycin (rifampicin or rifapentine) as TPT is not associated with an increased risk of TB which is resistant to those drugs.[352,353] Nonetheless, to minimise any potential risk, an individual's eligibility for 6HLfx will first require investigation for and exclusion of active TB – asymptomatic, normal CXR, negative sputum (if tested) – as well as positive evidence of infection – TST positive. Further, close monitoring of adherence as well as safety, with follow-up for development of active TB both during and after completion of TPT are crucial to evaluation of this intervention. The rationale for BCG catch-up is that it protects against infection and disease when given to non-immunised children and adolescents, and provides protection against leprosy, which is common in Daru.[112,521,526,527]

Our proposal builds on established experience in community engagement in Daru with 20 dedicated TB program staff, including six TB survivors who have been trained as peer counsellors and health promoters.[150] We conducted community consultations (starting November 2019) for this specific proposal with local health workers, community stakeholders and patient representatives to seek input into this research design, obtained strong support for the objectives, established a community advisory group and will continue collaboration with service delivery partners in Daru under the stewardship of the WPHA. There is now considerable experience with the screening of households on Daru for TB case detection as well as the provision of TPT with follow-up for eligible young child contacts of DS (as 6H or 3HR) and MDR-TB (as 6Lfx) (Chapter 5). Uptake and completion of TPT in young child contacts has been high with no serious adverse events reported. Our proposal also seeks to strengthen capacity for TB operational

research in PNG by providing opportunities for further training. This proposed implementation and health systems research will provide opportunity for additional operational research and postgraduate research training in TB and MDR-TB.

7.3 The Impact of COVID-19 pandemic and adaptations

This study was designed and planned for implementation prior to the COVID-19 pandemic. On April 16th, 2020, Western Province reported its first 3 cases of COVID-19, in Kiunga, North Fly District. As of February 22, 2021, there were 280 people diagnosed with COVID-19 and 11,246 tests performed. All cases have been in North Fly District with none in Daru town. The community was initially in lockdown in March–April 2020 but has since been without restrictions. Efforts have been made for prevention measures such as physical distancing and COVID-19 safe practices in line with the PNG National Department of Health and WHO advice. There were major changes to the delivery of the Western Province TB program in 2020 due to the impact of the COVID-19 pandemic on travel, health systems and community. As for elsewhere in PNG and many countries in the Western Pacific region, these changes have resulted in major disruptions and setbacks to TB programs.[91] Despite the challenges, the Western Province TB program has adapted rapidly to minimise the impact on quality of care and patient outcomes – TB case notification rates and treatment outcomes have not changed (Chapter 3). TB program staff have been mobilised to provide support to the COVID-19 response across synergistic areas and in consultation with the WPHA. Significant community engagement has occurred through the TB peer counselling team, who have provided COVID-19 education and health promotion at the individual, household and community level. Protocols and SOPs were developed for COVID-19 screening and infection control at Daru Provincial Hospital.

However, in 2020, the scope of the TB program activities had to be curtailed (Chapter 3). TB active case finding, including household contact screening and management with TPT were halted to reduce the burden on health services and health staff. International TB specialists and staff who supported these activities were demobilised to their home countries in March 2020. Activities pivoted to support COVID-19 vaccination rollout, community engagement and maintenance of essential TB services. A reduced staffing team was maintained until 2022. In February to March 2022, the international team was remobilised and TB services including contact tracing and TPT for young child contacts were re-instated. This proposed study will consider the COVID-19 context and adapt

depending on the risk assessment and any PNG protocols. Adaptions implemented from 2020 to 2022 include:

- Infection prevention and control protocols in health facilities and for healthcare interactions (including personal protective equipment provision) – implemented
- Integration of COVID-19 screening and testing into TB – implemented in health care facilities
- Expand community engagement programs for TB to include and integrate education on COVID-19 – implemented
- Accommodate and support vaccination program for COVID-19 – implemented. The WPHA TB program has supported the delivery of the primary course of COVID-19 vaccination in South Fly District. We will work closely with WPHA and the community in Daru in the preparation, implementation and uptake of any further delivery of COVID-19 vaccines when this is required. This may require a temporary pause to implementation research activities for TB, and diversion of resources, especially trained heath staff, to other priorities.
- People can receive BCG vaccination at the same time as or any time after other inactivated vaccines, including COVID-19 vaccination. However, it is recommended not to have another vaccine *in the same arm* as BCG for 3 months post administration. People eligible for a COVID-19 vaccination (including boosters) as per PNG guidelines will be referred to routine services to be offered this. If they accept, they will then be offered BCG vaccination following informed consent, as part of the study protocol.

7.4 Aims and Objectives

The primary aim of this prospective research project is to assess the impact of a comprehensive package of existing and novel tools on age-related TB incidence on Daru.

We hypothesise that a comprehensive community-based intervention package with high acceptance and uptake, that systematically detects and treats active TB in all Daru residents as well as provides prevention (TPT or BCG vaccination) in eligible residents without active TB who are 5-34 years, will reduce the incidence of new TB cases in

children, adolescents and young adults (<35 years) Daru by an estimated 30% after 2 years.

The SWEEP-TB project includes the following objectives:

Objective 1: Detect and Treat – To implement systematic screening of all Daru residents to detect and treat prevalent disease due to drug-resistant and drug-susceptible TB

Objective 2: Prevent – To provide TB preventive therapy or BCG vaccination to eligible Daru residents under 35 years of age to prevent infection and disease due to drug-resistant and drug-susceptible TB

Objective 3: Evaluation & Knowledge transfer – Evaluation of the intervention, conduct operational research training in TB including MDR TB for PNG researchers and support higher degree research student supervision

Expected outcomes: The evaluation of the comprehensive package (objective 3) will use a multi-dimensional framework with specific, measurable indicators:

1. The primary outcome measure will be impact on epidemiological burden. Using routine surveillance and notification data, the age-related burden of TB and MDR-TB will be compared between the 24-month pre-intervention and the 24-month post-intervention period
2. Secondary outcome measures are:

2.1. Description of the demographic and clinical characteristics of the participants
2.2. Age-related prevalence of TB infection
2.3. Quality and coverage of care by cascade of care analysis for TB detection, treatment and prevention
2.4. Impact on age-related treatment outcomes for TB disease and infection at 12 and 24 months and factors associated with unfavourable outcomes.
2.5. Acceptability and feasibility of the intervention using structured checklist assessments and description of implementation using a plan-do-study-act framework (PDSA)
2.6. Effectiveness of a novel combination TPT regimen on incident TB in those who received TPT compared to those who did not, at 24 months follow-up post-treatment

2.7. Safety of the novel combination TPT regimen with active drug-safety monitoring (aDSM)
2.8. Health system resource requirements and cost-effectiveness of the comprehensive intervention

7.5 Research Design and Methodology

7.5.1 Study Design

Prospective, community-based, population cohort, mixed-methods implementation study.

The study will be embedded within the routine TB program and a discrete public health intervention (community-wide screening) from the WPHA TB program, supported by partners (Burnet Institute and World Vision). The study will utilise quality improvement process, whereby the study inputs and activities (trainings, tools, systems, human resources) will be integrated into the routine program, as was the case for our pilot study on household contact tracing and TPT provision for young child contacts. The study will collect and utilise routine programmatic data (primary outcome, secondary outcomes 1, 2 and 5), which includes household enumeration, active case finding, treatment and TPT for young children of DS-TB index cases. The implementation of objective 2 (prevent) will require the collection of enhanced individual level data for the administration of TST, provision of the novel combination TPT regimen and assessment of safety through active TB drug-safety monitoring and management or aDSM – for this individual consent will be obtained for this novel intervention.

7.5.2 Study setting and population

The study will be conducted in Daru, an Island in the South Fly District and the capital of the Western Province of PNG. Daru is estimated to have 19,397 in 2021 residents and a crude population density of 2,500 persons per km^2, with overcrowded living conditions.[133,152] The most recent census recorded 2,019 households with an average household size of 7.5. The PHA leads the TB program in Western Province with support from the NTP and international partners. Daru Provincial Hospital, a 100-bed provincial referral hospital, is the only facility in the South and Middle Fly Districts of the Western Province to provide diagnosis and treatment services for MDR-TB, as the Daru TB Basic Management Unit. It has a large TB department with a 40-bed inpatient unit and one ambulatory TB clinic.

Daru is divided into four wards, each with elected representatives (members, also known as community chiefs). Daru has five community treatment sites or clinics, known as DART sites, which cover the four wards. Community-based healthcare workers - nurses, community health workers and treatment supporters - provide TB medications, education and counselling, and treatment enablers as food. Community treatment supporters provide adherence support and monitoring for all DR-TB and selected DS-TB patients. Household contact screening of TB cases was introduced in 2016 with an initial focus on case-finding and provision of TPT to eligible young child (<5 years) contacts.[397]

The study population will be residents of Daru, defined as planning to live in Daru for at least 12 months at the time of screening and provide assent.

The study aims to be as inclusive as possible. All eligible members of the community will be actively encouraged to participate through community engagement, education and the informed consent process. This would include priority groups such as age (children, adolescents and older persons), pregnant women, people living with disabilities (including cognitive impairment and mental illness) and people living with HIV. See section 4.3 for ethical issues regarding specific populations.

7.5.3 Sample Size

The size of the study population is directly determined by the size and age-related demographics of the resident population of Daru Island at the time of the study. Final impact of the comprehensive intervention will be by analysis of trends of age-related TB case notifications and incidence in Daru residents over time, with comparison of total and age-related incidence of active TB (DS and MDR) in a 24-month post-intervention period (2025-27) with 24 months pre-intervention and pre-COVID (2018-19).

As our study design is pragmatic with a similar approach for the entire population, the lack of a “non-intervention” arm for comparison means that it is not possible to discern the impact of the comprehensive implementation package or of individual components of the comprehensive package (e.g. enhanced active case detection vs TPT vs BCG). However, it will be possible to compare characteristics and outcomes between age-matched sub-populations for the uptake and completion of TPT. It is expected that from the Daru census population of 19,397 the study population who identify as residents will be 15,518 (80%) among whom 13,966 (90%) residents are anticipated to accept enhanced screening for active disease. Based on recent programmatic incidence data

and data from systematic screening for disease in households of TB cases in this community, the yield of active TB is expected to be ~2%, i.e. around 280 new TB cases detected. Of 13,686 people without active TB, 9,854 (72%) are estimated to be under 35 years and among them 4,927 (50%) eligible for TPT with an estimated 20% who decide to leave Daru i.e. 3,942. Among them, around 2,759 (70%) are estimated to commence TPT following informed consent and 1,183 (30%) decline. Assuming a 7% risk of developing TB during follow-up, the study will have 100% power and 95% confidence to determine a 60% reduction to 2.8% in those receiving TPT.

7.5.4 Study procedures and implementation

7.5.5 Study algorithm

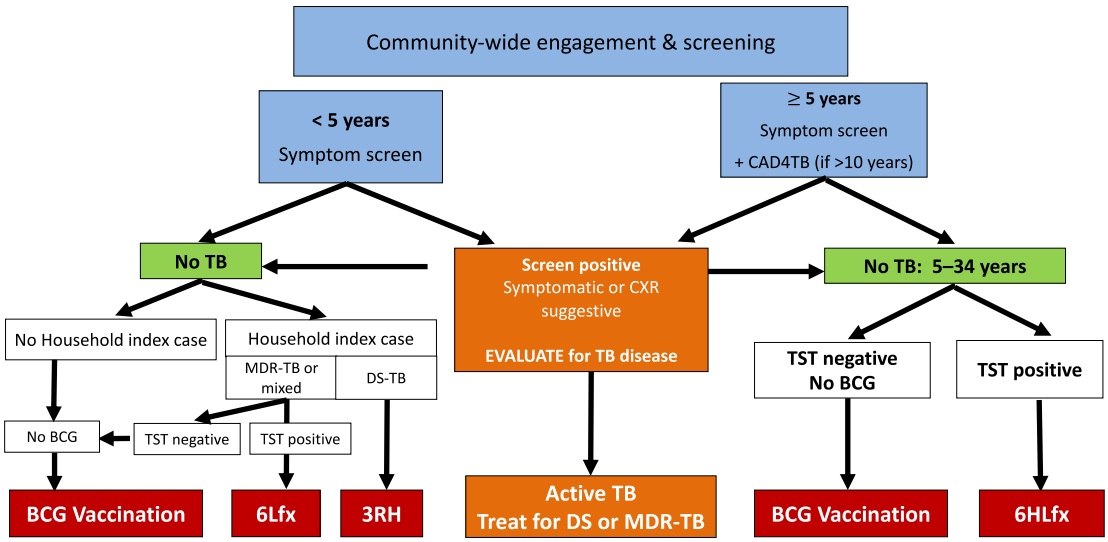
An overview of the approach to screening and management of participants is provided as an algorithm Figure 7.2. Households in Daru will be screened systematically via wards. In addition, as per current program protocol, household contacts of index cases will be screened within 2 weeks of diagnosis of the index case, irrespective of ward residence. Specific mobile screening sites will be considered for particular settings and groups, as advised by the community advisory group and WPHA, for example schools, fisher people, business houses.

Active TB detection will occur via symptom screening and digital CXR with the CAD4TB artificial intelligence system that has been used and validated in Daru by NDoH and WHO. It will be explicitly clarified to those residents who decline to participate in the study that they will continue to receive full TB services as and if required – that is passive case detection. If active TB is detected, referral will be made to commence treatment. Those without active TB will be offered participation in the novel interventions following informed consent for the prevention interventions. Participants above 5 years and up to 34 years who consent will be offered TST, unless they have had TB or TPT in the previous 12 months. Residents aged between 5 and 34 years without active TB AND with evidence of infection (i.e. TST positive) will be offered TPT as a six-month regimen of daily isoniazid and levofloxacin (6HLfx), following a separate informed consent, with the 6HLfx regimen offered irrespective of whether there is a known close contact. This is to provide treatment for infection with DS and/or MDR-TB strain. Consistent with current practice in Daru, young children (< 5 years) without evidence of active TB will only be offered TPT if there is a known household contact with bacteriologically confirmed TB, and the TPT regimen offered will depend on the drug-susceptibility/resistant profile of that index case:

3HR if contact has DS-TB (rifampicin susceptible on Xpert Ultra) or 6Lfx if contact has MDR/RR-TB.

As a result of consultation with the community advisory group and WHPA, participants will be provided conditional food vouchers for participation in screening (12 kina per person) and for completion of TPT (60 kina per person per course), as is received for active TB treatment. This is in keeping with Daru-specific community expectations and enablers provided for those on active TB treatment.

Figure 7.2 Screening, diagnostic and management approach for SWEEP-TB



7.5.6 Implementation timeline

A pre-implementation or planning phase is required to engage with health authorities and the community. This re-commenced as part of WP TB program activities in April 2022, post disruptions from COVID-19 and while all ethical approval is sought. The proposed comprehensive intervention has approval from the WPHA, NDoH and WHO and Burnet Institute has been tasked to lead implementation. There is strong community support for this intervention and from stakeholders, including from the mayor, community leaders and TB survivors. Community consultations were conducted in December 2019 and led to the establishment of a community advisory group (CAG) to guide community mobilisation and implementation. The CAG has self-named “TB Nanito Kopia Kodu” which translates as “the voice to kill TB” and have continued regularly (monthly) meetings from 2022. The terms of reference for the CAG are in Appendix 7.2.

Community wide health promotion is ongoing with a focus on the need to treat infection ("sleeping TB"), as well as to concurrently detect and treat disease of both DS and MDR-TB. This will include a specific and comprehensive campaign, led by the PHA, TB community engagement team and CAG, that will include health promotion materials (posters, leaflets, flipcharts), events (sports, churches), radio messages and multimedia communications (animations or videos), community sessions from leaders (elected representatives - mayor, ward members - and community leaders), school education, group and individual sessions – as has been successfully implemented in our previous pilot study (**Chapter 5**). A community engagement handbook has been developed and translated into Kiwai**.** These materials are in Appendix 7.3**.**

The community-based electronic data capture system will be developed, configured and tested in Daru, linking to the existing WPHA TB program electronic medical record system (EMRS, Bahmni EndTB configuration 1.52; Thoughtworks, Chicago, IL, USA) as described in section 3.6 below. A mobile data collection application for screening on hand-held devices (tablets) will be developed.

In preparation for the previous systematic screening, household enumeration (residents, age, sex) and geospatial mapping were performed in 2017. This will be updated by the project team through ward members and household heads, confirming the number of people living in each household. Verbal consent to incorporate this information into the routine WPHA TB database will be obtained from household heads, as data will not be individually identifiable. Households will be assigned unique identifiers (UIDs)and issued with a household card with their UID in text and as a QR code.

SOPs for SWEEP-TB have been developed, expanding on the current SOPs for household contact screening and management and includes procedures for household mapping, recruitment and consent, screening and evaluation for active disease, TST placement and reading, BCG vaccination, TPT and follow up, adverse event identification, management and reporting, data entry and management and reporting**.** SWEEP-TB tools and, forms and registers have been developed that are additional to the National TB program, such as the SWEEP screening and diagnostic form, TPT enrolment and monitoring form, cards for TST, TPT and BCG vaccination and referral forms.

The implementation timeframe for this proposed project will depend on relevant approvals, the evolving COVID-19 pandemic and the availability of dependent resources,

including staff (WPHA and Burnet). The plan is to implement the proposed project in 3 phases:

Phase I: June 2023– December 2023

Phase I is a 6-month feasibility (pilot) intervention of the comprehensive intervention package that will utilise a quality improvement process and action research methodology to establish a functional model for expansion in phase II. Activities will pause in December, prior to the commencement of phase II.

An expanded community-based team, including medical, nursing, radiography, health promotion, logistic, data and administrative staff will be recruited and trained. The research team will receive training in health education, informed consent, disability inclusion for research, safeguarding training (including working with children) and clinical / public health procedures including TB screening, diagnosis, TST placement and TPT. The tools and forms will be reviewed, translated, and adapted as required in this phase, using both paper based and electronic forms.

Screening will commence in wards and locations determined by team in consultation with ward members, WPHA and CAG. Each ward will have multiple SWEEP sites (temporary clinics) identified with several areas for screening, education, digital x-ray, clinical assessment, TPT and vaccination. In addition to paper-based tools, a community-based electronic data capture system will be established. Data to inform phase II will be collected such as uptake of screening, prevalence of infection in non-household contacts without active TB, uptake of TPT, population movement and formative research will be conducted on operational feasibility and acceptability of the model of care. The recording and reporting tools, data systems and multi-dimensional evaluation framework will be reviewed and finalised for phase II based on lessons learned.

Supporting health system components such as supply chain, laboratory and the health information system will be tested, and any deficiencies addressed. Study governance, safety procedures and reporting will be tested and reviewed.

Regular monthly meetings, including with community representatives and health workers, will review challenges and identify potential solutions to overcome barriers for implementation. Strategies to engage the community and reach high coverage will be developed, with a focus on priority populations identified by the CAG – workers, people with disabilities, the elderly, adolescents and students, church members and prisoners.

Phase II: January 2024 – December 2024

Phase II will involve a 12-month implementation period of the comprehensive intervention package where the entire island will be systematically screened through households and targeted screening. The age-related screening algorithm, implementation approaches and tools will be informed by phase I. The mobile clinic will be situated in each of the five currently established community treatment sites for approximately a 3-month period each. Routine prospective household contact screening and management will be integrated with SWEEP and continue in households of newly diagnosed DS and MDR-TB cases throughout the intervention. This will complement the proposed screening and management of non-household contacts, so that there is no duplication of the intervention package for island residents. The screening and mobile clinic will provide a service for all Daru residents at any time, including those not resident in the ward site where the mobile clinic is situated. Follow-up will involve 6 monthly reviews of all participants commenced on TPT for 24 months from initial recruitment and screening. This is in addition to follow-up of those receiving treatment for active TB or TB infection (as below).

Phase III: January 2025 – December 2026.

Phase III will sustain an enhanced model of care over a 24-month period. The program will continue a strengthened model of community-based active case detection and TPT for household contacts of all ages through TST testing. The final algorithm will be informed by the phase II results. Evaluation of the intervention will include operational research projects delivered through our established SORT-IT course with capacity building and knowledge transfer to PNG researchers. Cost-effectiveness analysis will be performed. Final impact of the comprehensive intervention will be by analysis of trends of age-related TB case notifications and incidence in Daru residents over time, with comparison of total and age-related incidence of active TB (DS and MDR) in a 24-month post-intervention period (2025-26) with 24 months pre-intervention (2021-22) and pre-COVID (2018-19).

7.5.7 Study procedures by objective

Objective 1: Detect and Treat

Systematic screening of all Daru residents to detect and treat prevalent active TB due to drug-susceptible or drug-resistant TB disease

Each household will be assigned an UID, and global-positioning system (GPS) coordinates will be recorded for the purposes of identifying households and individuals for follow-up. The Daru community will be sensitised to the intervention and its purpose through extensive community engagement and multi-modal health promotion. Approval to commence screening in the ward will be obtained from ward members. Verbal consent for screening will be obtained from the household head and people in the household. The screening officer will be conversant in the local languages of all potential participants (Tok Pisin and Kiwai). Following agreement to participate and verbal consent for TB screening, each participant will be assigned a unique screening registration number, which will be linked throughout all care episodes, and a registration form will be created.

Systematic screening for young adolescents and adults (10 years and older) will include: a symptom screen (any of persistent cough, fever, weight loss, haemoptysis or night sweats); clinical assessment for TB (including of nutritional status and examination for extrapulmonary TB); and mobile chest radiography using CAD4TB for those who are negative on symptom screen.

The optimal age-related use of CXR in screening asymptomatic, HIV-uninfected people aged 5-34 years to rule out active TB is not clear.[167] While the CAD4TB system has not been endorsed by WHO in in children under 15 years, it has previously been used in Daru in adolescents and adults (≥10 years) by NDoH and WHO for systematic screening. The company (Delft Imaging) has performed validation in children over 4 years and evaluation is ongoing in several studies. The CAD4TB system will be used in young adolescents and adults ≥10 years as this group commonly present with adult-type TB disease on CXR.

WHO guidelines recommend that asymptomatic young child contacts or PLHIV do not require CXR before TPT initiation.[9] It is likely that the same approach could be applied to all children (<10 years) with TBI without risk of amplifying resistance (i.e. not detecting sub-clinical disease due to the pauci-bacillary nature of TB in this age group).[516] Children (<10 years) will receive symptom screening and clinical assessment but those that screen negative and are well will not have routine CXR because of known low specificity, challenges of interpretation and very low yield for case detection, especially of bacteriologically confirmed TB, in asymptomatic children.[287]

A positive screen that leads to further evaluation for TB disease will be defined as the presence of any abnormal clinical findings for participants of all ages:

- TB symptoms greater than 2 weeks: cough, fever or night sweats > 2 weeks
- Presence of haemoptysis
- Reported weight loss
- Undernourished on nutritional assessment (as detailed in the SWEEP study SOPs and Appendix 5.3)
- Any signs of extra pulmonary TB (lymph node enlargement, spinal deformity)
- Additional symptoms for children: failure to gain weight, reduced playfulness, not reaching milestones
- Abnormal CAD4TB score for adolescents and adults (threshold to be determined during calibration)

If screening is positive, sputum specimens for Xpert Ultra will be collected and tested for *Mycobacterium tuberculosis* (MTB) and rifampicin resistance (RR). As per current practice, RR-positive samples will be transported weekly via air to the Central Public Health Laboratory in Port Moresby for culture and drug susceptibility testing, as described previously[404] and Xpert MTB-XDR for the detection of mutations associate with isoniazid and fluroquinolone resistance. Those who screen positive by clinical evaluation or CAD4TB but in whom specimens for detection of MTB are negative or unavailable, including children, will undergo further clinical evaluation. Evaluation of children under 10 years with clinically presumptive TB will be performed with digital CXR (CAD4TB is not validated for children <10 years) and other investigations as determined by clinicians (e.g. gastric aspirate, lymph node aspirate or faecal Xpert Ultra).

If TB is diagnosed (bacteriologically confirmed via Xpert Ultra or clinically diagnosed), treatment will be offered and initiated at the community clinics. Medically unwell or complicated cases requiring hospital admission or those requiring hospital-based further assessment will be referred to Daru Provincial Hospital. Treatment will be provided according to the local standard of care and NTP guidelines for DS and MDR-TB. All TB cases are registered with the TB program and reported to the NTP. Treatment is delivered at community treatment sites with enablers (food packages), counselling and monthly medical review in an ambulatory clinic.

Objective 2: Prevent

Provide TB preventive therapy or BCG vaccination to eligible Daru residents under 35 years of age to prevent infection and disease due to drug-resistant and drug-susceptible TB

Through collaborative support to the district and provincial TB program and through our pilot health implementation research project (Chapter 5), we have established a model of community-based household contact screening and TPT for young child TB contacts. In 2020, these activities were interrupted and paused due to the COVID-19 pandemic. While TPT in young child contacts is important to protect this high-risk population from severe disease, the impact on reducing transmission is very limited compared to the potential of TPT for adolescents and adults.

In this proposal, residents of Daru who are screened but do not have active TB will be offered TST testing by a trained nurse and if positive, offered TPT following separate informed consent. Education and counselling will be undertaken. Treatment will be self-administered at home with ambulatory follow-up. The TPT management protocol will be age dependent. Young children (<5 years) without evidence of active TB will be offered TPT as per contact history: 3HR if exposure to an index case with DS TB, or 6Lfx if index case has MDR-TB or close contact with both MDR-TB and DS-TB. For ages 5 to 34 years, all TST-positive individuals without active TB will receive 6HLfx irrespective of contact history. For 35 years and older, TPT will not be offered routinely, but if requested, there will be an individual evaluation and decision to treat considering the potential benefits versus risk, including increased risk of toxicity in this age group (especially risk of hepatotoxicity with isoniazid).

All patients on TPT will be actively monitored until completion, including for adverse events, adherence and development of symptoms at 1, 2, 4 and 6 months. Participants under 35 years, who have no active TB and are TST-negative, will be offered BCG vaccination if they have no known previous BCG or scar (as per PNG guidelines). Participants with positive TST who decline TPT or are ineligible, due to exposure to an index case with fluoroquinolone resistance, will be informed of their infection status and counselled. Contacts of fluoroquinolone resistant-TB will be managed individually as determined by clinicians, outside the study protocol. Education regarding TPT and symptoms of TB disease and the importance of early presentation to health services will be emphasised and provided by an experienced team of health promoters and peer educators. The TB clinicians and program may manage contacts of fluoroquinolone resistant index cases or individuals with multiple household contacts on a case-by-case basis and offer TPT such as 3HR as a clinical decision outside of the study protocol. All participants without active TB at screening, irrespective of TST status or TPT uptake, will be evaluated for the development of active TB if symptoms develop, and routinely every

6 months for the 24 months following initial screening. The follow-up schedule is displayed in Table 7.1.

TST and TPT will be administered as per our previous study protocol and the program in Daru has considerable experience with both. TST involves an intradermal injection of 0.1 mL of 2 tuberculin units (TU) of tuberculin purified protein derivate (PPD) RT 23 in the volar aspect of the forearm for participants aged 12 months or above. The dose for participants under 12 months is 0.05mL. The TST result will be measured by the study nurse 48-72 hours post injection. TST will be considered positive when the transverse diameter of induration is ≥10 mm regardless of BCG vaccination status or ≥5 mm in a contact with HIV infection or severe malnutrition. Weight-based drug dosing for TPT for children <5 years, older children and adults is displayed in Table 7.2, Table 7.3 and Table 7.4.

Table 7.1 Follow-up schedule for TB preventive therapy in the study intervention

Time	**Visit Purpose**	**Activities**
D0	Enrolment PT initiation	Baseline evaluation, TB screening, weight Education session: refer to counsellor if needed Prescribe TPT
M1	Assessment – Follow up	TB screening, weight, adverse effects, adherence, Review/refill medication
M2	Assessment – Follow up	TB screening, weight, adverse effects, adherence Education session: Review/refill medication
M3 (3HR)	Assessment - Outcome	TB screening Record outcome
M4 (6HLFX)	Assessment	TB screening, weight, adverse effects, adherence, Review/refill medication
M6 (6HLFX)	Assessment and Delivery of Outcome	TB screening Record outcome
M 12 (6HLFX)	Assessment – 6-month post completion	TB screening, weight
M15 (3HR)	Assessment	TB-free survival (1 year post completion)
M18 (H6LFX)	Assessment	TB-free survival (1 year post completion)
M24	Assessment	TB-free survival

Table 7.2 Weight-based dosing for preventive therapy for children < 5years who are contacts of DS-TB index cases

DOSING OF RIFAMPICIN/ISONIAZID RH should be given at a dose of 10 mg/kg together with Vitamin B_6.				
Weight Range	**R/H Tablet (75/50 mg) dispersible Tablet**		**Pyridoxine/ Vitamin B_6 dose(25 mg)**	
	Daily Dose	**# of tablet per day**	**Daily Dose**	**No. of tablets per day**
4.0-7.9 kg	75/50 mg	1 tablet	12.5 mg alternate days	0.5 tab alternate days
8.0 – 11.9 1111.9 kg	150/100 mg	2 tablets	12.5 mg	0.5
12.0– 15.9 kg	225/150 mg	3 tablets	12.5 mg	0.5
16.0 –24.9 kg	300/200 mg	4 tablets	25 mg	1

Table 7.3 Weight-based dosing for preventive therapy for children < 5years who are contacts of MDR/RR-TB index cases

Weight	**Levofloxacin** **100 mg dispersible tablets**	**Daily dose (mg)**
3-4.99 kg	0.5 tab	50 mg
5-6.99 kg	1 tab	100 mg
7-9.99 kg	1.5 tab	150 mg
10-11.99 kg	2 tabs	200 mg
12.0– 24.99 kg	1 tablet	250 mg

* Tablets may be crushed and mixed with a standard syrup, if tolerated.

Table 7.4 Dosing for preventive therapy for older children ≥5 years and adults who are TST positive and eligible for TPT

Weight	**Levofloxacin 100mg, 250 or 500mg tablets**	**Isoniazid 100mg tablets**	**Pyridoxine 25mg tablets**
7 – 9.99	150 mg	100 mg	12.5 mg
10 – 11.9 kg	200 mg	100mg	12.5 mg
12.0– 15.9 kg	250 mg	150 mg	12.5 mg
16 – 24.9 kg	250mg	200mg	25 mg
≥25 kg or adult	500mg	300mg	25 mg

Objective 3: Evaluation & Knowledge transfer

Evaluation of the intervention, conduct operational research training in TB including MDR TB for PNG researchers and support higher degree research student supervision

A multi-dimensional framework will be used to evaluate the intervention:

1. The primary outcome measure will be impact on epidemiological burden. Using routine surveillance and notification data, the age-related burden of TB and MDR-TB will be compared between the 24-month pre-intervention and the 24-month post-intervention period
2. Secondary outcome measures are:
   2.1. Description of the demographic and clinical characteristics of the participants
   2.2. Age-related prevalence of TB infection
   2.3. Impact on age-related treatment outcomes for TB disease and infection at 12 and 24 months and factors associated with unfavourable outcomes.
   2.4. Quality and coverage of care by cascade of care analysis for TB detection, treatment and prevention
   2.5. Acceptability and feasibility of the intervention using structured checklist assessments and description of implementation using a plan-do-study-act framework (PDSA)
   2.6. Effectiveness of a novel combination TPT regimen on incident TB in those who received TPT compared to those who did not, at 24 months follow-up post-treatment;
   2.7. Safety of the novel combination TPT regimen with active drug-safety monitoring (aDSM)

2.8. Health system resource requirements and cost-effectiveness of comprehensive intervention.

Programmatic indicators from the routine surveillance system and additional data collected during SWEEP-TB implementation will be used to evaluate the quantitative primary and secondary outcomes (1, 2.1, 2.2, 2.3, 2.4, 2.6, 2.7). Programmatic documents such as meeting minutes, formative surveys and focus groups will be used as formative research to describe implementation, acceptability and feasibility (2.5).

A quality improvement method will be used to identify and implement solutions to gaps in the cascades of TB care using the plan-do-study-act (PDSA) cycle to facilitate ongoing reflection and improvement on the quality of the community-based detection and prevention of TB and MDR/RR-TB in Daru. A cascade dashboard will be developed and reviewed in monthly meetings with the implementing team. A standard meeting minutes document will be developed to capture key discussions and actions, as well as an issues tracker spreadsheet to capture operational and other emerging logistic issues.

To evaluate the policy relevance and scalability of the intervention, we will assess health system resource utilisation and conduct a cost analysis. We will measure all costs of care for participants, including commodities, staff time, other aspects of workflow, transport and supervision. Initial costs of training, infrastructure and equipment will be annualised over their expected lifespan and for anticipated staff turnover. The Optima TB model of the epidemic in Daru will be used to evaluate the incremental cost-effectiveness ratio and return on investment for the comprehensive interventions relative to current programs based on the TB disease burden. Optima TB is an open-source tool available online and is a top-tier model endorsed by the TB Modelling and Analysis Consortium (https://optimamodel.com/tb/applications.html).[528] The modelling tool has previously been used in Daru (Figure 7.1) and is currently being implemented in National Capital District. Data inputs for the model will be driven by the new epidemiological and programmatic data gathered through the study, and the updated model will also be used to guide decision making and advocacy toto support a sustainable and efficient response to TB within Daru. Moreover, the DR-TB transmission and programmatic parameterisation will allow for assessments to be conducted of the return on investment of applying similar comprehensive TB testing and prevention interventions in settings across PNG, allowing future business cases for investment to be developed.

We will conduct a SORT-IT training program in partnership with NDoH, UPNG and PNG IMR for selected participants (all PNG nationals) and topics focused on TB-related operational research training that evaluates projects including of MDR-TB in Western Province and other parts of PNG. Training, guidance and mentoring support will be provided from protocol development to national and international dissemination, building on previous success.[158] Selection of topics and participants will be guided by the national TB program (and its research advisory committee) to optimise capacity building and address priority implementation knowledge gaps. Several PNG researchers who completed the previous SORT-IT program will be engaged as junior facilitators. In addition, we will offer funding and supervisory support for a PNG national for a postgraduate degree in research (Masters or PhD) and as a "research champion." Our strong and collaborative institutional engagement with the NDoH, PNGIMR and UPNG will continue through the established biannual meeting of the PNG TB research advisory committee and annual dissemination workshops.

7.5.8 Data variables and collection

Data collection will occur through forms (tools and registers) that will be integrated into the TB program's electronic medical record system (EMRS). Household mapping and screening will be conducted by the implementation team on paper forms and an electronic mobile device that will be configured during the planning phase and phase 1. Active TB Treatment and TPT enrolment, monitoring and outcome forms and registers are paper-based and will be transcribed in the EMRS by data officers.

The registration data to be collected at screening includes - sociodemographic characteristics, history of previous or current TB treatment, BCG vaccination status and scar, medical history, TB risk factors (smoking, alcohol and drug use, diabetes), household ID and travel outside of Daru in the preceding 2 years and TB contact history – these are routine programmatic variables for active case finding. A research clinician will complete the evaluation, including review of history, symptom screen including for specific TB-related symptoms, weight and clinical findings. The data variables collected for diagnostic evaluation of TB include CXR or CAD4TB score, Xpert Ultra sputum (or other sample) results. All participants with a diagnosis following full evaluation of active TB disease – DS or MDR, bacteriologically confirmed or clinically diagnosed – will commence treatment with TB treatment register including date of TB treatment initiation, TB type and site, adherence monitoring, follow-up with weight, adverse events, and treatment outcomes. For those who do not have active TB, TST will be performed. As

described above, contact investigation of new index cases will occur concurrently. Those eligible for TPT, the following will be included on separate TPT register: date of TPT initiation, regimen, adherence monitoring, follow-up with weight, adverse events and treatment outcomes defined as complete (>80% doses taken), incomplete, not initiated, lost to follow-up, or treatment failure (i.e. TPT stopped) due to development of active TB, serious adverse event or death. TB treatment outcomes will be recorded as per routine program in the TB registers and EMRS. Outcomes for TPT will be recorded as per Table 7.5 for any participant that has had one dose of TPT.

Table 7.5 Outcome definitions for TB preventive treatment

Outcome	**Description**
Complete	The patient has completed TPT as prescribed. Completion is defined as completing 80% of scheduled daily doses* (144 of 180) without an interruption of greater than 60 days (ie within 240 days of commencement)
Developed TB	Active TB was diagnosed at any time while on TPT, following a baseline assessment that excluded active TB.
Died	Patient died for any reason while on TPT
Lost to follow up	TPT interrupted for 2 consecutive months (60 days) or more and the program is unable to make contact with the person. if >144 doses taken, assign outcome of complete
Treatment discontinued	A decision was taken to stop TPT by the clinician or patient, regardless of cause if >144 doses taken, assign outcome of complete Record reasons for discontinuation Adverse effect of medication or contraindication. Additional details: (a) Adverse effect of medication (b) contraindication Patient discontinued treatment, not an adverse effect. Additional details: (a) left Daru (b) Medical or social reason - specify (c) withdrew consent / did not wish to continue - specify (d) drug stock out – specific H or Lfx (e) other – specify (f) not recorded (3) Reassessed on clinical review as not eligible for TPT following initiation Additional details: (a) active TB diagnosed (b) not infected

Cascades of care will be adapted from existing frameworks and collected as aggregate and individual steps (cross-sectional and longitudinal).[170,290,529] For the TB case detection cascade of care analysis, the indicators include participants screened, evaluated, diagnosed, and commenced on active treatment, as well as time between each step of the cascade. For the TB prevention cascade of care analysis, variables include number

and proportion of participants screened, assessed for eligibility, and initiated on preventative treatment, as well as time between each step of the cascade. Acceptability of the intervention by participants and feasibility will be gathered from meetings with the CAG, focus groups with community members and research and implementation teams.

To describe implementation, program activities and the model of care will be identified from the SOPs, meeting minutes, reports and a study activity log maintained by the investigator team. Implementation will be described by engagement, TB detection and prevention, data systems and operational systems.

To assess health system resource utilisation, we will measure all costs of each model of care, including commodities, staff time, other aspects of workflow, transport and supervision. Initial costs of training, infrastructure and equipment, will be annualised over their expected lifespan and for anticipated staff turnover. These costs are available from the WP PHA and partner project budgets.

7.5.9 Data management

Data will be managed using the WPHA TB program's existing electronic medical records system (EMRS, Bahmni EndTB configuration 1.52; Thoughtworks, Chicago, IL, USA) which has been operational since 2017. The EMRS has modules for TB screening, diagnosis and treatment (active and TPT) and is utilised by treating clinicians to assist in the delivery of quality care and by the program managers to generate reports. The EMRS is maintained by data entry officers from the WPHA, and Burnet project team and is managed by the provincial TB program data coordinator. The EMRS is primarily a patient care system and has been utilised for routine reporting, quality improvement and operational research. The EMRS is owned by the WHPA. Technical support to maintain, configure and adapt the EMRS is provided by the Burnet institute under the existing MOUs with WPHA and NDoH which cover data utilisation and monitoring and evaluation.

Data is entered from paper sources (tools, registers and records). Paper sources include registers for presumptive TB, DS TB, DR-TB, TB laboratory, contact screening and TPT; as well as patient charts and forms for test results, patient follow up, counselling and register. Mobile data collection will be implemented allowing participant data to be entered onto mobile devices in the community. Internet-connected hand-held devices and laptops will be used to enter patient data on TB screening, investigation, diagnosis and preventive therapy directly into Bahmni.

The Bahmni EMRS is hosted on a secure server that is physically located at Daru Provincial Hospital (DPH). Devices used to access Bahmni must be pre-authorised and connected to the DPH network, or if not on-premises, must use a VPN connection with per-user credentials to remotely access the Bahmni EMRS for data entry. No patient data will be stored on the devices.

In the event of an internet or server outage, paper-based data collection will be used with the data then entered into Bahmni by trained data entry officers. Data on X-ray screening, including images, heatmaps and computer assisted detection scores will be collected on a dedicated CAD4TB box that can work offline. The CAD4TB box is a small computer that consists of a PACS server, a web server that hosts the CAD4TB software and the AI software for image interpretation. The images, scores and patient data will be regularly synchronised to a PACS server hosted on a server at DPH both as a backup and to make the data available to health care workers at the hospital who are involved in TB diagnosis, care and treatment.

A unique study ID will be assigned to each participant and will be given to the participant on a card or recorded in their health book. When data are extracted from the EMRS for study analysis a unique study analysis ID will be added to the data and all other identifying information will be removed to generate a non-identifiable data set. A separate key of unique study IDs to study analysis IDs will be kept in an encrypted electronic format accessible only to the principal investigator and used only if validation of data is needed. Data will be managed by the investigator team, project team and TB program staff for the duration of the study. The EMRS is hosted on a secure, dedicated server. Non-identifiable data will be extracted from the EMRS using SQL scripts (structured query language) in a delimited text format and imported into R v.4 (R Foundation for Statistical Computing, Vienna, Austria) with v.1.2.1 of the tidyverse package for validation and analysis.

7.5.10 Data analysis

Non-identifiable data will be generated from the EMRS as outline above, in a comma separated variable format. Analysis will be undertaken using Stata version 14. Categorical variables will be described by frequency and proportion. Numerical variables will be described by mean and standard deviation or median and interquartile range depending on normality assumptions. Differences in categorical variables will be tested by chi-square test and differences between numeric variables will be tested by unpaired t test or Wilcoxon rank sum test depending on normality assumptions. Cross-sectional

cascades for TB case detection and prevention will be expressed as numbers and proportions. Additional longitudinal cascades will determine the timing between cascade steps. The magnitude of the associations of clinical and socio-demographic characteristics with PT non- completion will be assessed using relative risk (RR) with 95% confidence intervals (CI). Level of statistical significance will be set at 5%.

The Optima TB model of the epidemic in Daru will be used to evaluate the incremental cost- effectiveness ratio and return on investment for the comprehensive interventions relative to current programs based on the TB disease burden. Optima TB is an open-source tool available online, which has previously been used in this setting (Appendix 7.1) and also in National Capital District. Data inputs for the model will be driven by the new epidemiological and programmatic data gathered through the study, and the updated model will also be used to guide decision making and advocacy toto support a sustainable and efficient response to TB within Daru.

The study analysis will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[507] As part of monitoring & evaluation for the project we will provide an annual report that will include metrics on knowledge transfer and capacity building, including numbers trained, post-graduate students enrolled, dissemination, publication output and policy change.

7.5.11 Safety Monitoring

The proposed “novel” combination regimen of isoniazid and levofloxacin daily for 6 months (6HLfx) is not novel in the treatment of active tuberculosis, both drug-sensitive and drug-resistant. Both drugs are registered and procured by the PNG NTP and can be given in combination for MDR-TB (shorter regimen or longer regimen). Use of levofloxacin as preventive treatment for MDR-TB is described in the 2020 WHO guidelines on TB preventive treatment.[159]

Rigorous safety monitoring of the proposed regimen is important, and we therefore propose regular active drug safety monitoring – as recommended in MDR-TB programs or as per a clinical trial – with real-time reporting to a Data Safety Monitoring Committee (DSMC, see Appendix 7.4 for terms of reference:). The DSMC will be established as an independent advisory group to supplement provincial and national aDSM systems, which may not be functional, and will specifically monitor:

(1) The frequency, severity and management of all adverse events that occur in individual study participants receiving TB preventive treatment, and

(2) The diagnosis and drug-resistant profile (if known) of any incident case of active TB disease that occurs from initiation of preventive treatment through to completion of study participant follow-up.

The DSMC will review quarterly study reports and may request additional interim data to further evaluate or determine any emerging risks such as frequency or severity in adverse events. The DSMC will report to the Western Province PHA and the National Department of Health - the National TB Program (NTP), the Medical Research Advisory Committee (MRAC) and the Pharmaceutical Services Standards Branch (PSSB) and to the co-principal study investigators.

The DSMC does not have the authority to stop the study or modify the protocol. The DSMC findings and reports will be used to inform decisions by the study investigators in consultation with partners and authorities (above) who receive the reports as to whether to continue or suspend the study, or to amend the protocol. The DSMC must protect the confidentiality of the study data and the results of monitoring. The DSMC will have 4 members and include experts in clinical medicine and epidemiology / clinical trials / drug safety, with 2 experts from PNG and 2 international experts. The DSMC will strengthen provincial and national aDSM systems through capacity building.

Possible adverse events (AEs) associated with the use of Levofloxacin and isoniazid include nausea and bloating, headache, dizziness, insomnia or tremulousness. Rare AEs include tendon rupture, arthralgias (can usually be treated symptomatically), QTc prolongation and hypoglycaemia. WHO recommends regular adverse event monitoring through clinical review during therapy with levofloxacin, however no specific laboratory monitoring is required at baseline or during therapy.[290] The severity of AEs will be graded by the using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. for severity of adult and paediatric AEs as recommended by WHO and in the PNG PMDT SOP for the use of new and repurposed TB drugs (Table 7.6).

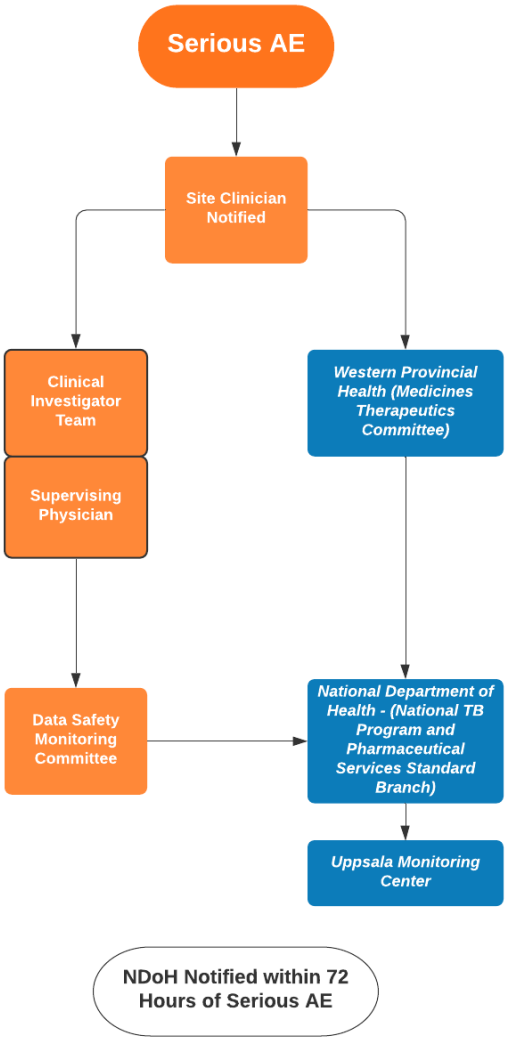
Table 7.6 Common Terminology Criteria for Adverse Events (CTCAE) grading for severity of adverse events

GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING	GRADE 5 DEATH
Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated.	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated.	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalisation indicated.	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent disability or death.	

Grading will be performed by the treating clinician, reviewed by the site investigators, with final authorisation by the principal investigator or delegate. The study will have a supervising local physician, and a supervising research physician, who is the Chief Physician in PNG and a co-investigator for clinical oversight and as a source of expert clinical advice and referral for any case or clinical query. A clinical expert group, exists in the TB program to provide expert clinical advice in MDR-TB treatment or TB preventive treatment, consisting of the DPH co-investigators and the supervising research physician, and DGP physicians.[496] All physicians are registered as specialist physicians in PNG with the medical board.

Treatment will be discontinued in the event of a grade 3 or grade 4 toxicity. Serious adverse events (SAEs - Grade 3, 4 and 5) will be reported to the principal investigators, WPHA (medicines and therapeutics committee) and NDoH (NTP, PSSB) and quarterly to the DSMC. Relevant ethics committee reporting requirements for serious adverse event reporting will be followed. The AEs reporting pathway are outlined in Figure 7.3.

Figure 7.3 Reporting pathway for Serious Adverse Events



The principal investigator will report any serious adverse events or suspected adverse events or reactions to the Licensing Authority (Health Secretary), National Department of Health via the PSSB and NTP within 72 hours.

7.6 Ethical Issues and Risks

7.6.1 Ethical approval

Permission to conduct the study and ethical clearance approval is being sought from the PNG IMR Institutional Review Board, Medical Research Advisory Committee and will also be sought from the Alfred Hospital Ethics committee in Melbourne, Australia.

7.6.2 Informed consent

Individual informed consent will not be required for the collection, management and analysis of routine programmatic data from the TB registers or EMRS that will be used for primary and secondary outcome measures 1, 2 and 4. There will be 2 stages of consent, information provision and verbal consent for all participants at screening and written consent for the sub-group of participants who will be eligible for TPT, as more detailed information is required on the novel combination regimen (secondary outcome measures 3 and 4). Consent will be sought from all potential participants or their guardians if children under 18 years or unable to provide consent.

Trained study staff will be responsible for obtaining informed consent from participants/guardians as appropriate. A participant information sheet and consent form are attached in the Appendix 7.5. They will be available in English and Kiwai. Study staff will ensure the participant/guardian is aware of study procedures and risk and will provide ample time to ensure participant's/guardian's questions are answered. As per PNG requirements, participants whose age is below 18 years will require an adult guardian or parent to provide consent. In addition, assent (affirmative agreement to participate) will be sought from children and adolescents aged 8 to 17 years. Illiterate participants (or those unable to sign) will have the consent form read aloud to them by a researcher. If a person then consents, the researcher will sign the consent form and note that verbal consent was given, and a witness or guardian will be asked to countersign.

In Daru, English and Kiwai are the main languages spoken and read. All study material will be made available in these two languages, and copies provided to participants/guardians. Consent may be withdrawn by any participant or guardian at any time, and participants will not be required to provide a reason. Those participants withdrawing consent will be able to continue accessing health services outside of the study and standard of care. Participants who are commenced on TPT but who withdraw their consent to participate in the study will be required to cease the study treatment and continue current standard of care.

Addition considerations for consent of people with disabilities, cognitive impairment or mental illness are described in section 7.6.6.

7.6.3 Specific populations

The study aims to be as inclusive as possible. All eligible members of the community will be actively encouraged to participate through community engagement, education and the informed consent process. This will include key population and/or groups vulnerable to TB risk such as children or older aged people, pregnant women, people living with disabilities, people living with HIV or other comorbidities such as diabetes.

7.6.4 Children and young people

This research will involve children and young people, including people who may be sick with TB, who are vulnerable members of the population. As the study involves interventions in detection and prevention beyond current PNG standard of care, voluntary written informed consent is sought from the parent/guardian when the participant is a child. In PNG this is defined as 15 years or younger.

Children and adolescents are at higher risk of TB infection in Daru, therefore TB screening, treatment and TPT provides individual benefit. Participation in the study provides an opportunity to protect their health and contribute to reduction in TB transmission in the community. The research will advance knowledge in several key areas such as optimal TB screening approaches, further evidence for TPT for MDR-TB and community-based health service models that reach and are accepted by children and young people.

The TB program in Daru has long standing experience in delivering child-centred TB services including a family-based model, child-friendly spaces, educational and informational materials and clinical protocols and guidance developed under the supervision of paediatricians. To ensure the safety, emotional and psychological security and wellbeing of children are protected, the counselling team will be available. Education regarding TPT and symptoms of TB disease and the importance of early presentation to health services will be emphasised and provided by an experienced team of health promoters and peer educators

Burnet has a Safeguarding Code of Conduct that all staff, volunteers, consultants and children must sign. There are also organisation-wide policies on Child Protection and Preventing Sexual Exploitation, Abuse and Harassment. Tailored annual training on child counselling approaches, tools and techniques and child protection training has been conducted with Burnet counselling staff and peer counsellors from Daru. The training

covers both the definition and practice of child protection, identification of forms of child abuse and neglect, the laws in PNG around child protection and referral pathways, and the Burnet policy on child protection and reporting processes. Staff are mandated to undergo a National Police Check however as it often takes months, all new employees must complete a Statutory Declaration stating either that they have never, in Papua New Guinea or another country, been convicted of an offence or, if they have been convicted of an offence, setting out the details of that offence. Statutory Declarations must be witnessed and signed by a Commissioner of Oaths. Staff need to be registered to the Medical Board of Papua New Guinea for their health profession which initially requires a police check.

7.6.5 Pregnant Women, the Foetus and Newborns

The inclusion and participation (with voluntary informed consent) of pregnant women has been considered, and it was assessed that the potential benefits outweigh the potential harms and that risks can be mitigated. Pregnant women are eligible to be participants in the research project and will provide informed consent in the 2 stages – verbal consent for screening and written consent if eligible for TPT. There are 2 interventions we have considered with specific additional risk to be considered for pregnant women – chest x-ray screening and the provision of TPT for those eligible. This study will provide TPT to women <35 years with evidence of infection (TST positive) to prevent TB, thereby potentially providing benefit for the mother and her fetus/newborn.

There is evidence from studies in UK and Sweden that pregnancy is associated with a two- to three-fold increased risk of developing TB. TB during pregnancy usually presents after 20 weeks or the early post-partum period.[61,331] TB in pregnancy has been associated with an increased risk of both maternal, foetal and neonatal morbidity and mortality.[330] The risks include stillbirth, preterm birth and IUGR as well as direct transmission to the foetus (congenital TB) or newborn.[530] Pregnancy-related TB disease is also very challenging to detect early and so often presents late resulting in poorer outcomes for mother and foetus or newborn.[531] The peak age prevalence of TB in Daru is 15-34 years, and therefore it is not uncommon to diagnose and treat TB and MDR-TB in mothers in that setting. From 2018 to 2022, 2.6% (12/444) of women have been pregnant while on MDR-TB treatment in Daru (program data, unpublished).

While TB treatment outcomes for pregnant women with TB are favourable, including for MDR-TB, there is a greater benefit for the mother and foetus in preventing the

development of TB through early detection (screening) and TB preventive treatment (TPT).[532,533]

Early TB detection of active TB through screening is a strategy to reduce the adverse outcomes associated with maternal TB. The WHO recommends TB screening for pregnant women when the prevalence in the general population is greater than 100 cases per 100,000 population, using chest radiography and/or symptom-based screening.[167] While studies have shown that symptom screening has poor sensitivity in pregnancy (HIV-infected women), there have been limited studies of the additional yield of chest x-ray.[330]

Chest x-ray of a pregnant women has been deemed by the WHO not to pose a significant risk to the foetus provided good practices are observed and the primary beam is targeted away from the pelvis.[167] Given there is low radiation risk to the mother and foetus with regards to the chest x-ray at the screening stage, and it is unlikely that all women screened will know their pregnancy status, or be willing to disclose it, our approach includes the following to ensure informed consent and risk mitigation for female participants;

1. Participants will be prompted to inform staff about pregnancy status during consent, the pre chest x-ray screening interview and prior to the chest x-ray. There will be visual aids and a verbal prompt from research staff which will ensure appropriate privacy and confidentiality for women.

2. Informing participants that there is a very small risk to undergoing chest x-ray during pregnancy, and that they can opt out for any reason without telling us the reason.

If active TB has been excluded, there are no harms to the administration of TST in pregnant women. In pregnancy women who are HIV-positive and have a positive TST, TPT is recommended.[159] In non-HIV infected women, current international guidelines provide limited advice due to the limited evidence of TPT in pregnancy.[159] TB guidelines in Papua New Guinea do not have any recommendations (positive or negative) for TPT in pregnant women. Preventive treatment can be administered during pregnancy after a risk-benefit assessment.

In the Daru setting, given the extremely high rates of TB and MDR-TB transmission, there is more benefit than risk for TPT i.e. the risk of TB is greater than potential adverse effects. In the study, this will be managed through individual consent and an operational research framework, including safety assessments. Two anti-TB drugs are proposed as a "novel" regimen for TPT – 6 months of daily levofloxacin and isoniazid for women who are TST-positive and <35 years. However, neither of the drugs alone are novel and both have been used to successfully treat TB and MDR TB in pregnant women, including in Daru. There is no known or published evidence of risk from either drug causing foetal abnormalities – teratogenicity in the first trimester. Given the well-established risks to the foetus and newborn if a woman develops TB during pregnancy, using treatments to prevent TB in a pregnant woman with TB infection that are not contraindicated in pregnant women and that have an established favourable safety profile is considered to be a much lower risk to the foetus than the development of TB in the mother.

Isoniazid is safe to use in pregnancy (category A, Australian Therapeutic Goods Administration, TGA).[345] Rifampicin is considered safe to use in pregnancy, although monitoring of liver function tests may be required in the third trimester (category C, TGA). There is limited data on the safety of prolonged fluoroquinolones in pregnancy. Moxifloxacin (same generation as levofloxacin) is category B3 (TGA) and from the limited to data available, has not been associated with increased risk of congenital teratogenicity.[345] One meta-analysis of observational studies including 2800 pregnant women exposed to fluoroquinolones found no differences in birth defects, spontaneous abortion or prematurity compared to unexposed pregnant women.[346]

Routine antenatal care will continue and is offered through Daru Provincial Hospital. If there are any medical issues or concerns, participants will be immediately referred to antenatal services. Pregnant women will undergo the same standard procedures and follow up as other participants. However, additional risk mitigations in the research protocol to protect the health and well-being of pregnancy women and the foetus will be instituted. These are:

- Questions asking participants if they are pregnant during enrolment, x-ray screening and during the written consent process prior to TPT.
- Pregnant women can opt out at any stage and will continue to receive care that is required
- Shielded chest radiography

- Integration of TPT follow up and antenatal care services and providers with a dedicated clinic for follow up
- Additional monitoring during TPT – liver function tests at baseline and monthly during routine antenatal care visits.
- Additional education, education and counselling support will be available to pregnant women on active TB treatment and TPT if required. Information regarding TB screening will be displayed at the antenatal clinic.

7.6.6 People living with disabilities, cognitive impairment or mental illness

Disability inclusion is part of routine care in the TB program in Daru, supported by the Burnet Institute which is an international development non-government organisation (NGO) accredited with the Australian Department of Foreign Affairs and Trade. The Burnet has a disability inclusion policy that sets standards regarding the approach to disability in development programs and health research. The TB program staff in Daru, through the Burnet Institute have received disability inclusion training from a specialist NGO in 2022 (CBM Australia), resulting in the development of a disability inclusion action plan. As part of the action plan, training across the whole team and discussions on adapting the action plan to the Daru context will occur. In addition, the WPHA TB program and Burnet team have a long-standing collaboration with the local disability partner organisation (DPO) in Daru, Callan Services, who have supported TB patient needs. The research team members (Burnet Institute) have received specific safeguarding training as per the Institute's policies in disability inclusion, child protection and SEAH (sexual exploitation, abuse, harassment). Additional training on disability inclusion in research will be provided for research team members who will be obtaining consent, interacting with participants and providing care or counselling. This training will be conducted by consultants from the University of Melbourne who have expertise in this area.

People living with disabilities will be consulted and engaged in research design where possible, including via membership of the community advisory group. Disability inclusion will feature in community engagement, health promotion activities and engagement with stakeholders to increase awareness of its priority. People with disabilities will be offered the opportunity to participate in the research project with appropriate consent and safeguards. In Daru, support is offered in the form of counselling and social support and through linkages to community-based NGOs, World Vision and Callan Services. Participants will be receiving the standard of care available in Daru, to ensure the best

available health outcome. Study participants may have non-TB health issues or complaints. The research team will refer these health issues to the relevant program health care worker or team member and the TB counselling team engaged if required to accompany or provide additional support.

Counselling staff involved in support for participants are trained in support for people with disabilities and in mental health awareness. Education tools and processes will be developed with consideration for the full spectrum of capacity and comprehension with images and visual aides used as much as possible. A video or animation will be developed for the consent process. Support of caregivers or family members may also be utilised to assist in ensuring participants are able to understand the study processes and TB information. In addition, a plain language statement will be developed to complement the participant information and consent forms (PICF, Appendix 7.4). Researchers also work in small teams to ensure the privacy of the participant. All communication related to the research will be provided in accessible formats. Information will be shared in a way that participants can understand.

Cognitive impairment, intellectual disability or mental illness will be assessed by trained members of the research team that is screening individuals. Information on the participant's capacity may also be provided by caregivers or family members. A decision aide (Appendix 7.4) that is included in the consent process and form, has been developed and adapted with the support of disability inclusion experts and from the Research for Development Impact guidelines and report.[534] If the initial routine screening questions will indicate comprehension issues and the participant's preferred language will be rechecked at this point to eliminate language barriers as the cause (a translator in their preferred language will be engaged if this is the case). If language comprehension is not the cause, the participant's cognitive, intellectual, and mental capacity will be assessed by trained staff. If the participant agrees, an assessment will still be undertaken to assess the extent of their comprehension, an internal capacity to consent checklist will be used (developed with University of Melbourne) to establish understanding and capacity.

The interview will proceed if there is no concern that informed consent might not be able to be provided, and if the participant does not need a support person to assist them with communications. If a support person is required, they will be asked by the participant to assist them in an interview. If a guardian, trusted family member or carer can assist the participant with an interview, the participant can be provided with an easy-to-understand

information form to ensure the participant understands the research and their associated rights. The interview will not proceed if a trusted family member, guardian or carer is unavailable. An additional field on the informed consent sheet will capture the assessment of the person obtaining consent. This process will be tested with people with disabilities and the CAG during the feasibility phase.

7.6.7 Potential risks and mitigations

Specific issues relating to this study include community engagement and education, informed voluntary consent amongst adult and child participants, risks associated with research participation especially amongst semi-literate participants, ensuring optimal clinical care as appropriate, careful monitoring for and appropriate management of drug-related adverse events and the secure management of de-identified data. See Table 7.7 for the risk management plan.

Table 7.7 Risk management plan

Potential risk	**Mitigation**
Temporary discomfort during tuberculin skin test (TST)	Informed consent; follow up at TST reading visit.
Allergic reaction to TST	Informed consent; educate and advise to present to hospital if concerned; follow up at TST reading visit.
Skin infection due to TST	Prior to the injection, skin will be cleaned with an alcohol skin swab or chlorhexidine antiseptic solution; follow up at TST reading visit.
Adverse effect to TPT (Isoniazid-Levofloxacin) There has been extensive use of individual components (isoniazid and levofloxacin) in large populations of adults, adolescents and children with known safety profiles.	All participants eligible for PT will be informed of possible side effects before providing consent. Participant information sheets will be provided outlining possible side effects and action required. First dose will be administered in the presence of a health care worker. All participants receiving treatment will be followed up monthly during treatment by the study team and will undergo clinical assessment and adverse events assessment. Management of adverse drug reactions will be as per existing procedures and protocols in PNG, noting that levofloxacin and isoniazid have been in use for MDR-TB treatment since Daru Provincial Hospital commenced its MDR-TB program (2011 or prior), noted in section 3.8 “Safety Monitoring”. Adverse events will be graded for severity using the CTACE scale.[535] Treatment will be discontinued in the event of a grade 3 or grade 4 adverse events. Serious AEs (grade 3, 4 and 5) will first be notified to the site clinician (site investigator, Mr Gabriel Kama, Dr Marukutira), who will report to the supervising physicians (Dr Baleo and Dr Maha), principal investigators and the clinical investigator team (Dr Margaret Kal, Prof Steve Graham, Dr Khai Huang, A/Prof Suman Majumdar – all registered specialist physicians in PNG). The investigators will also notify the WPHA (medicines and therapeutics committee) and NDoH – NTP and PSSB. The NDoH will be notified within 72 hours of a serious AE. A data safety monitoring committee established specifically for this trial. All serious adverse drug events will be independently reported by the site clinician firstly to the supervising physicians and investigator team and then on to the to aDSM committee, who will meet quarterly to review (*figure 3*) Prospective pharmacovigilance will be conducted and reported to the DSMC quarterly. Relevant ethics committee reporting requirements for severe adverse event reporting will be followed. The reporting pathway is outlined in figure 3.
Blood and body fluid exposure	Local infection control policy will be followed. All sputum samples will be collected in an area away from others, including the health care worker. The samples will be handled with gloves and placed into designated container for transport. Injecting equipment will be single use and will be disposed of immediately after use in a sharps disposal container. TST injections will occur in an allocated space away from others especially children to minimise risk of needle stick injury.

Potential risk	Mitigation
BCG risk	BCG is a live attenuated vaccine that usually causes a local reaction (ulcer +/- axillary lymph node enlargement) that is temporary and self-healing with a scar. Along with the potential benefits, this common and expected reaction will be explained when offering BCG to those who are eligible – child or young adolescent, no evidence of TB disease or infection, no previous BCG – and agree to be vaccinated. BCG is extremely safe and disseminated disease is rare. However, people with severe immunosuppression, such as people living with HIV who are not receiving antiretroviral therapy, are at risk. Therefore, BCG will not be given to those with known or suspected immunosuppression – but rather offered investigation and management as appropriate.
Study participant requiring emergency medical care (including from an adverse event)	On Daru Island, emergency services are available 24h a day and, due to the small land area, are accessible by all Daru residents. In addition, a medical officer is always on call for unwell patients. All unwell patients will be referred to and managed by existing health services in the WPHA.
Loss of confidentiality and stigma	Community screening and data collection is a potential risk to privacy and confidentiality. The TB program team have had years of successful experience in engaging with the community in Daru.
Loss of data through computer malfunction or theft	Electronic data will be backed up on password-protected external hard drive.
Incomplete registers and data	Ongoing, regular weekly research staff meetings with continuous quality improvement through review of indicators, achievements, gaps.
COVID-19 infection risk to health care workers	PNG National guidelines and protocols for COVID-19 infection prevention and control, including personal protective equipment will be adhered to during the study. Testing will be available as per the routine program.
COVID-19 impact on travel and movement	The pandemic will pose a risk to domestic and international travel – for staff in the program and investigators. This may be through quarantine, lock downs or border closures. This risk cannot be mitigated as government regulation will be followed.
Legal and indemnity risk	Clinical study staff employed by the Burnet institute have appropriate medical indemnity insurance cover for this study. WPHA and NDoH staff are covered by Government of PNG policies. The study will not limit the ability of participants to pursue damages through the existing pathways available in relation to health care services in PNG.

7.6.8 Study benefits

The main potential benefit for the community is that early case detection and treatment of TB (active and latent) can reduce TB transmission in the community. The community has already been engaged and participated as part of contact screening, and community participation will be required in ongoing and future efforts to improve the effectiveness of

case detection, management and prevention. There is a broader benefit in increased knowledge and awareness of TB for the community.

Specific individual benefits include the diagnosis and treatment of TB disease for those not yet identified and preventing the development of TB disease in those with latent TB infection.

Health care workers in Daru will benefit through the implementation of evidence-based practice, research and the capacity strengthening initiatives detailed above. The aim is to build a sustainable workforce capacity, so those who are trained will in turn train others in PNG.

Local researchers, including those listed as co-investigators, have been involved in the planning of this project and will be co-leading the research from initiation to completion with support from the PI and senior international co-investigators. They have been and will be involved with capacity development in the development of a research protocol and tools; data collection, management and analysis; providing interim updates; and presentation of findings for oral and written peer-reviewed dissemination.

The skills and knowledge developed by local staff as part of this research project will provide a strong foundation for local researchers to undertake formal operational research training utilising actual data form the project. There is funding support for a PNG higher degree research student.

7.7 Reporting and Dissemination

A plain language statement of one page that includes the main findings and messages from the research will be developed in English and Tok Pisin, and made available to patients, families and community groups. Knowledge translation of findings will occur through dissemination and reporting to the provincial and district health authorities, community and hospital health staff, and to the national TB technical working group. Study tools, including for evaluation and data management, will be made available to adjust and support operational implementation and research for other settings in PNG, and to provide input for NTP registers.

Regular updates with interim reports of project progress, as well as updates as requested, will be presented to key stakeholders: in Daru at least quarterly including to

WPHA, South Fly District TB Program, World Vision, Daru Provincial Hospital; and in Port Moresby at least biannually to NTP, NDoH, members of the TB research advisory committee including UPNG, PNG IMR and WHO, and members of the national TB technical working group.

Dissemination will occur through submissions to present interim findings at the annual PNG Medical symposium, Australian TB Research meetings and the Union's annual Global TB conference. The final report of findings will be reported back to the IMR IRB and MRAC for endorsement before dissemination of the final study outcomes and analysis. Manuscripts will be submitted for publication in peer-reviewed journals including the PNG Medical Journal.

7.8 Timeline and Resourcing

7.8.1 Timeline

The timeline below (Figure 7.4) assumes ethical approval is obtained in quarter 4, 2022.

Figure 7.4 SWEEP-TB study timeline

Calendar Year		2022				2023				2024				2025				2026			
	Quarter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Aim	Activity																				
	Pre-implementation phase and planning																				
1, 2	Phase I: Feasibility (comprehensive package)																				
1, 2	Phase II: Implementation (comprehensive package)																				
1, 2	Follow-up period																				
1, 2	Phase III: Enhanced model of care																				
1, 2	Analysis and impact assessment																				
3	Knowledge transfer (research training)																				
All	Knowledge transfer (dissemination) workshops																				

7.8.2 Funding and Resourcing

The Burnet Institute is the study sponsor and will be responsible for initiation, management and arranging financing for the study. Burnet is an independent

nongovernmental organisation and medical research institute with headquarters in Australia and a long-term country office in PNG.

Specific funding for this implementation research and research capacity building proposal has been obtained through the Australian Government (Medical Research Future Fund GNT 1201008) to the Burnet Institute (CIA Prof Graham). A/Prof Majumdar is supported by the National Health and Medical Research Council (NHMRC) postgraduate scholarship.

Implementation of the programmatic and research activities will be supported by the WPHA and partners – Burnet Institute and World Vision who are funded by the Australian Government.

The South Fly District TB program is funded by the Provincial Government, National Department of Health and Australian Government through grants via PATH (PNG Australian Transition to Health) to partners Burnet Institute and World Vison.

This programmatic support and funding include:

- WPHA and Daru Provincial Hospital – staff, diagnostics, treatments, personal protective equipment, office space, outreach services, community
- Burnet's RID-TB (Reducing the Impact of Drug-resistant TB) project in Western Province, PNG provides technical assistance, training and operational support in Daru.
- World Vision International (Stop TB in Western Province) – community treatment program, treatment supporters, community health promotion

Chapter 8: Discussion

Tuberculosis is the leading infectious disease killer globally, causing 1.25 million deaths in 2023. [1] Multidrug- and rifampicin-resistant TB (MDR/RR-TB) represents a critical threat to achieving the WHO End TB strategy goals.[19] Despite advances in diagnostics and treatment, global progress has been insufficient, with TB incidence declining by only 1% annually from 2015-2023 when 10% was required to meet 2035 targets.[92,536] The End TB Strategy emphasises comprehensive detect-treat-prevent approaches, yet implementation evidence from high-burden MDR/RR-TB settings remains limited. The key bottleneck to ending TB is the limited implementation of currently available prevention strategies, particularly TPT, which remains largely restricted to household contacts despite evidence that transmission extends beyond households in high-burden settings. Whilst much can be achieved with existing tools, new tools such as point of care testing and vaccines to detect and prevent both disease and infection have the potential to increase implementation efficiency and accelerate progress towards TB elimination.[111,181,537–539]

This thesis examines the implementation of such comprehensive strategies in South Fly District, Papua New Guinea - one of the world's highest burden MDR/RR-TB settings - providing crucial evidence for scaling prevention strategies beyond household contacts to community-wide interventions in similar contexts globally.

This thesis aimed to address the policy-practice gap and generate evidence for prevention strategies that reduce the burden of TB, including MDR/RR-TB in Daru, SFD, a remote setting in PNG, with applicability to other high burden MDR/RR-TB settings.

8.1 Main Findings

Three operational / implementation research studies were conducted, embedded in the programmatic TB response in Daru, South Fly District, Western Province to evaluate interventions to detect, treat and prevent TB, including MDR/RR-TB from 2014 to 2022 (Chapters 3, 4, 5). This led to the design of a novel comprehensive community-based TB screening and prevention study protocol from 2021 to 2023 (Chapters 6, 7). The findings demonstrate a clear evolution in strategies from control, towards ending TB- from emergency response and treatment and care optimisation, through understanding the socio-ecological determinants, to developing comprehensive prevention approaches that extend beyond conventional household-based interventions.

8.1.1 Detection and treatment outcomes of TB in SFD

This thesis documented one of the longest and most comprehensive evaluations of TB program implementation in a high-burden MDR/RR-TB setting, spanning nine years from emergency response through systematic strengthening to pandemic resilience (Chapter 3).

A retrospective cohort study revealed very high case notification rates of TB and MDR/RR-TB case notifications in SFD with alarming levels in Daru. Several epidemiological factors – high TB burden in children and adolescents, high proportion of new cases among MDR/RR-TB – coupled with previous molecular epidemiology indicate ongoing intense community transmission of DS and more importantly, MDR/RR-TB, despite programmatic interventions. The concentration of cases in Daru residents suggests the island remains a focal point for transmission, which may be enhanced by the cyclical migration of residents to and from the mainland SFD, where there is limited case detection.

The most significant finding was the dramatic improvement in treatment outcomes achieved in a fragile health system setting. Treatment success rates increased from 53% in 2014 to consistently above 85% from 2016 onwards for both DS-TB and MDR/RR-TB.

This success was underpinned by several key factors: implementation of mWRD, introduction of more effective MDR/RR-TB treatment regimens and care delivered through a person-centred community-based model, community partnership and engagement, strengthened data systems and operational research capacity building. This was achieved through sustained technical partnership and support to WPHA's TB program by Burnet Institute through the RID-TB project.

The program demonstrated resilience during the COVID-19 pandemic, maintaining treatment outcomes. This resilience can be attributed to the robust health systems strengthening that occurred in the preceding years, though the pandemic's impact on case detection highlights remaining vulnerabilities in the system.

However, the findings also reveal a critical limitation: while high TB treatment success rates (>85%) can be achieved through focused programmatic interventions, these alone are insufficient to interrupt transmission and reduce TB incidence. There is an urgent need for enhanced interventions to reduce transmission, particularly in Daru. The current investments have no sustainability when the TB burden is so high. Further,

decentralisation of services beyond Daru are very limited, and social and structural determinants of TB transmission remain unaddressed.

8.1.2 TB care journey and socio-ecological determinants dimensions

The qualitative research (Chapter 4) employed a socio-ecological framework to explore the lived experiences of 20 people with TB in Daru, revealing how individual, community, and institutional factors intersect to shape TB care experiences and transmission risk.

At the Individual level, participants' TB knowledge was grounded in family experience and was not a major barrier care-seeking and utilisation. At the community-level, the benefit of the evolution of the model of TB services from the rigid DOT approaches toward flexible, person-centred community-based models was experienced by participants. The introduction of peer counselling represented a key innovation that complemented existing family and kinship support systems. However, traditional wantok support systems were strained under the burden of TB care, creating complex dependencies and stigma. Significant socio-economic barriers to TB care remained in this highly vulnerable community, despite the provision of food and material (voucher) support.

At the institutional level, the centralisation of TB services created profound inequities with life-threatening consequences for people from mainland villages who faced lengthy journeys and very high transportation costs, forcing families to separate and abandon support networks.

Households in Daru were characterised by complex, fluid arrangements shaped by cyclical migration, with multi-generational overcrowding creating dense living environments conducive to TB transmission. This socio-ecological analysis revealed that households are simultaneously key determinants of TB transmission and key units for intervention. Despite household fluidity, understanding these kinship-based dynamics proved essential for designing prevention interventions that work within existing social structures, directly informing the household-based engagement and interventions.

8.1.3 Scaling up prevention strategies: from household to community-wide approaches

This research represents the first comprehensive evaluation of TB prevention strategies in a high MDR/RR-TB burden setting, demonstrating the evolution from household-focused to community-wide prevention approaches (Chapters 5, 6, 7).

The prospective implementation study (Chapter 5) evaluated community-based household contact investigation between October 2017 and December 2020, including PNG's first implementation of novel TPT regimens: rifampicin and isoniazid (3HR) for contacts of DS-TB index cases and levofloxacin (6Lfx) for contacts of MDR/RR-TB index cases.

Key prevention findings included:

- High screening coverage and yield: 4,988 household contacts screened with 90.1% coverage and screening yield for active TB of 3.2%, highest in young children under 5 years (6.0%)
- Successful TPT implementation: Moderate TPT uptake (43.1%) but high completion rates (83.3%) across all regimens, with good tolerability and minimal adverse events across all TPT regimens, including the novel 6Lfx regimen
- Complex transmission patterns: 13.2% of contacts had multiple index cases, challenging conventional household-based prevention approaches
- High infection prevalence: Higher TB infection prevalence in MDR/RR-TB contacts (49.4%) compared to DS-TB contacts (36.8%), with infection prevalence increasing with age, particularly in early adolescents

The findings support the feasibility of implementing WHO-recommended TB prevention strategies in remote, resource-limited settings and demonstrate the value of community-based approaches. However, they also revealed critical gaps in current prevention strategies.

Chapter 6 provided a critical analysis of household-based contact investigation approaches, identifying lessons learned and potential solutions. Overall, an acceptable and feasible community-based model of contact investigation was established. Successful elements were the adaptation of tools and an electronic data system, development of participatory education materials, child-friendly and family-centred model, engagement of local health workers and establishing a community advisory group

to inform and advise the TB program. Challenges include the application of households as the unit of intervention for determining an individual's exposure to TB, including MDR/RR-TB, as the basis for TPT provision. The analysis highlighted that a focus exclusively on household contact investigation may not be optimal in Daru's socio-cultural context and where high levels of community MDR/RR-TB transmission occurs. This led to the innovative proposition that prevention strategies must extend beyond household contacts to community-wide approaches to achieve meaningful epidemiological impact.

Chapter 7 presents the research protocol for SWEEP-TB (Systematic Community-Wide Engagement & Elimination Project for TB), representing a paradigm shift from household to community-wide TB prevention. This comprehensive strategy combines enhanced case detection, effective treatment, and novel community-wide prevention approaches featuring the novel 6HLfx regimen - a combination of isoniazid, levofloxacin, and pyridoxine designed to protect against both DS and MDR-TB in mixed exposure settings.

While SWEEP-TB results are outside the scope of this thesis, early implementation data demonstrate proof of concept of the feasibility of community-wide screening and prevention implementation. As of June 2025, 16,242 Daru residents were screened, 2,001 (12.3%) screened positive with CXR and/or symptoms, 264 (1.6% among screened) were diagnosed with active TB (79.5% microbiologically confirmed, and 20.5% clinically diagnosed). Of these 54.5% (n=144) reported no TB symptoms.

After active TB was ruled out, 9,349 (59.1%) were eligible for TB infection testing with TST and 7,847 (83.9%) received TST placement. Among them, 3,173 (40.4%) had positive TST results. A total of 3,128 (98.6%) were eligible for TPT and the majority, 2,421 (77.4%) accepted and initiated TPT. Among 1,485 individuals with outcomes, 677 (45.6%) had completed TPT, 535 (36.0%) were lost to follow-up, and 269 (18.1%) had discontinued treatment.

This research generates novel evidence for comprehensive TB prevention strategies in high MDR/RR-TB burden settings, highlighting critical implementation gaps in current WHO guidelines and providing a framework for scaling prevention beyond household-based approaches to achieve the population-level impact necessary for ending TB.

8.2 Limitations, challenges and lessons

8.2.1 Methods and generalisability

This thesis conducted operational and implementation research on TB that was embedded in a public health program in Daru, South Fly District, PNG and has several limitations, inherit to the methodology and context.

First, the methods were descriptive (qualitative) and observational (retrospective cohort, prospective implementation), rather than experimental. As such, the quantitative analytic approaches, in particular those that assessed and compared trends, characteristics or risk factors were prone to bias inherent in observational data. The pre-post design for evaluating programmatic interventions (Chapter 3 and Chapter 5) does not fully account for unmeasured factors that may have influenced outcomes measured for TB detection, treatment and prevention. This may have included health service or system developments, changes in population characteristics or population movement that may have influenced TB transmission, health seeking behaviours and service utilisation and outcomes, rather than the public health or TB interventions themselves. However, the cohort sizes are large, with long study durations (9 years for Chapter 3 and 30 months for Chapter 5), and there has been detailed description of public health interventions. The lack of control groups or randomisation meant that causation could not be definitively established between specific interventions and outcomes, although the temporal association of improved treatment outcomes with program implementation provides supporting evidence.

The specific limitations of the qualitative study (Chapter 4) included the sample size of 20 people with TB as a cross-sectional study. While appropriate for this design, it was prone to selection bias (positive experiences), desirability bias, missed people who didn't access services or were lost to care, may not have captured experiences of people outside Daru in remote villages and did not account for changes over a longer time.

Second, data quality and completeness are key limitations of routine programmatic surveillance and operational and implementation research in resource-limited settings (Chapter 3 and Chapter 5). Internal validity was constrained by data quality issues inherent to routine program data, particularly in earlier periods (2014 to 2015) when paper-based records were used. While the electronic medical record system improved data capture from 2016, there were still missing data and data quality issues. Data checks and validation were used to counter these issues for the datasets analysed for

this thesis. As there is no national identification system, there was the potential for re-identification issues and age and residence misclassification, due to patient recall and/or awareness. This may have impacted tracking participants across multiple episodes of care, i.e. re-screening and re-treatment may not have been accurately identified.

Key risk factors for TB were not available in the routine surveillance system and would inform a better understanding of TB epidemiology in SFD (Chapter 3). This includes collecting information on nutritional status, co-morbidities including diabetes mellitus, smoking and alcohol history and data on education status and socio-economic index. These may have been potential unmeasured confounding variables in the assessment of risk factors for unfavourable outcomes in the cohort study (Chapter 3).

While most variables had excellent completeness (<1%), HIV status (13.7% unknown overall; 38.7% in 2015 declining to <5% by 2018) and treatment outcome ascertainment showed temporal improvement reflecting programmatic strengthening. The missingness was temporal in nature, with later years (2016-2022) offering more reliable estimates. This was due to programmatic strengthening (systematic case detection and management protocols) and data systems strengthening rather than other sources of systematic bias. Given the low HIV prevalence (<3%), minimal missingness for most variables (<1%), and systematic temporal improvement in data completeness, more complex analytical approaches such as imputation would be unlikely to meaningfully alter findings or interpretations.

These methodological and data limitations had cross-cutting implications for comparability and causal inference across studies. At the programmatic level, health information system constraints—including absence of unique identifiers and incomplete capture of key variables—limited individual-level longitudinal analysis and intervention attribution. At the research level, observational designs without control groups and non-random missing data patterns necessitated reliance on population-level comparisons and temporal associations rather than definitive individual-level causal inference. These challenges reflect the practical realities of implementation research in resource-limited settings with evolving health systems. However, the documented temporal improvements in data completeness, large cohort sizes, and detailed intervention descriptions provide robust evidence for programmatic impact, while the persistent limitations highlight ongoing needs for health information system strengthening as foundation for both service delivery and research.

Third, the thesis is addressing the problem of sustained high levels of TB transmission, and this has not been directly measured through approaches such as a serial prevalence survey for active disease or TB infection.[197] Rather TB case notifications are used which only captures individuals who access diagnosis, is influenced by variations in clinical diagnosis and changes in case-finding approaches, including systematic screening. Case notification rates are based on population denominators and estimates from the PNG national census. The last census was conducted in 2011, with the 2021 figures only extrapolated. Specifically, the population of Daru has substantial uncertainty due to population mobility between Daru and mainland villages. There have been two surveys for enumerating households and residents of Daru, prior to the systematic screening conducted in 2017 (14,444, unpublished) and as part of SWEEP-TB in 2023 (22,099 people).[520] However, person-to-person transmission of MDR/RR-TB in Daru has been confirmed by molecular epidemiology[148] and high TB notifications have been established by epidemiological data (Chapter 3). There will be an opportunity to compare TB infection data from the household contact cohort with community and contacts (including matched households) from SWEEP-TB as a serial TBI prevalence survey for example in children under 10 to assess recent infection and therefore transmission.

The generalisability of findings is both enhanced and limited by the unique study setting. Daru's extremely high TB and MDR/RR-TB burden, combined with its geographic isolation and health system constraints, provides valuable insights for other high-transmission settings. However, the intensive technical support and resources provided through the emergency response may not be replicable in many contexts. The successful implementation of community-based care was facilitated by Daru's small geographic size, which may not translate to larger urban or dispersed rural settings. The socio-cultural findings are difficult to generalise beyond Western Province, even within PNG due to the diversity among the various ethnic and tribal groups and belief systems. The public health findings, however, are generalizable to other parts of PNG, and have lessons for similar high-burden settings in the region (Pacific Islands), but also beyond.

8.2.2 Implementation challenges and lessons

Research in the health system and development context

A significant challenge, but also opportunity was conducting research within a public health response that involved a fragile health system (WPHA, Government of PNG) and international development program (Government of Australia), involving partner agencies such as WHO, other donors (USAID) and non-government organisations.

As described in Chapter 3, the Western Province health system is characterised by chronic shortages of health workers at all levels and frequent turnover of staff. Significantly, this included medical and public health leaders and led to disrupted governance, coordination and leadership. A solution to this was building resilience and community-based health delivery systems that promoted models of task-shifting and simplification. Sustained technical support was also required, and often supplementation of critical service delivery roles (clinical) when there were gaps. This was a major barrier to research, as resources were often directed from research to service delivery support. Dedicated human resources were required for contact investigation (screening and TPT provision) and operational research.

The health system fragility was also seen in terms of interrupted supply chains and laboratory systems. Culture and drug susceptibility testing was frequently disrupted at the national reference laboratory and national TB drug and TST stock-outs occurred, affecting both clinical care and research outcomes. Implementation research activities, including the studies in Chapters 5 and 7 (SWEEP-TB) are dependent on these systems.

The research was embedded within a donor-partner funded TB response which both enabled access to resources and technical expertise but also created sustainability challenges. In particular, the TB response was vulnerable to funding cycles and changes in donor priorities. A key strength was the long-term institutional partnership established between the Burnet Institute (RID-TB project) and the WPHA leadership and NDoH, which enabled a clear joint strategy and plan that set an ambitious goal of reducing TB transmission and incidence and included operational and implementation research. The embedding of research within public health and development programs created both opportunities and challenges. It enabled real-world evaluation of interventions and supported the introduction of innovations but required careful balance between research rigour and programmatic needs- requiring clear translational outcomes and ownership of the work by those in PNG.

The programmatic strengthening described in Chapters 6 and 7 built substantial local capacity through community engagement, health worker training, and systems infrastructure. However, sustainability of comprehensive TB programming remains critically dependent on continued financing, with resilience to recent international development assistance disruptions uncertain. Domestic resource mobilisation and integration of TB services into core health systems will be essential for long-term sustainability, though this transition remains incomplete.

Data systems and management

The implementation of an electronic medical record system (EMRS) in 2016 was transformative for both clinical care and research but required sustained technical support and capacity building. It was established primarily as a clinical care tool that enabled program monitoring (reporting) and operational research. Data quality improved over time with local capacity building and support to the data management team. Operational challenges included the infrastructure and system requirements – server, internet connectivity and information technology support. The specific EMRS, Bahmni, was chosen as it was open source and in use for TB clinical trials at the time. However, the EMRS was overly complex for the setting in terms of resource requirements and skills to maintain it. This complexity and lack of WPHA funding precluded handover or transition.

Data management and analysis was a challenge and key lesson, particularly in the prospective implementation study (Chapter 5). Key data were incomplete or missing, and this was due to the file structure (data entry forms) of the EMRS, not aligning with the paper-based forms. This was addressed through primary data quality checks, which I conducted in Daru, and adjustment to the analysis approach. These issues indicated the need for more resources for quality checks and training of data entry officers (or use of researchers with higher levels of skills) with the existing EMRS that is designed to collect high quality individual level data. Alternatively, a more simplified approach and system could be implemented- with current plans to conduct a review of options. The lack of unique identifiers for individuals in PNG was challenging and meant that it was difficult to link people across stages in the TB cascade of care. Clinician recording of adverse events was suboptimal. These lessons were learned in the development of the approach and data systems for SWEEP-TB, which have been simplified, and appropriately resourced. The experience highlighted that robust data systems are essential for both service delivery and research in such settings but require significant investment in infrastructure and human resources.

COVID-19 disruption

The COVID-19 pandemic had substantial impacts on the research program. It interrupted the follow-up of young child contacts receiving TPT (Chapter 5) and delayed the implementation of SWEEP-TB by almost two years. However, this disruption led to valuable learning about health system resilience and adaptation of service delivery models. The TB program's established and sustained community engagement and

community-based workers for contact investigation proved valuable for COVID-19 response, including vaccination and health promotion, demonstrating the importance of building community-based systems and community-centric public health approaches. The EMRS was also valuable for monitoring patients and the program.

8.3 Significance and Contribution

This research represents one of the most comprehensive and longest evaluations of the implementation of a detect-treat-prevent approach in a remote, high-burden MDR/RR-TB setting. Prior to the emergency TB response, there was limited local TB research to guide implementation in PNG's unique context. This a unique contribution that not only provides crucial insights for responding to the enormous issue of TB in South Fly District, Western Province but generates evidence with local and global significance for ending TB. Most importantly, the findings reveal that even excellent treatment outcomes may be insufficient to interrupt transmission without comprehensive prevention interventions - driving the evolution toward the innovative community-wide approaches described in this thesis.

8.3.1 Local significance: Papua New Guinea

National policy and practice change

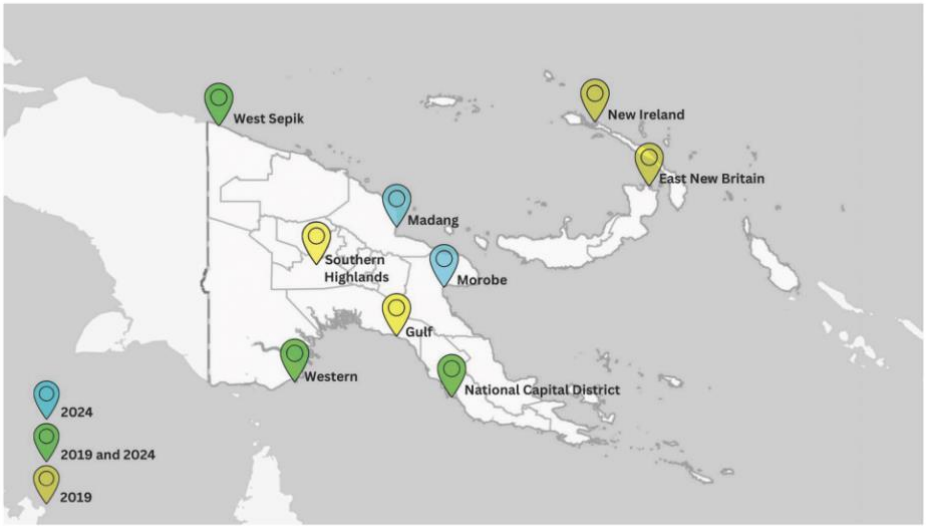
The development of successful community-based models of care and translation of research findings into practice in SFD has been an important exemplar for PNG. Based on the successful MDR-TB treatment outcomes documented in this thesis, the SFD model directly informed the PNG national guidelines and standard operating procedure for community-based MDR-TB treatment and care (2017), resulting in the scale up of the locally validated, evidence-based treatment regimens and community-based care models. In addition, the peer counselling model and contact investigation approaches and tools have been adopted in Port Moresby (National Capital District), the national hotspot MDR-TB. Training and exchanges on TB management and models have occurred with other provinces - Morobe, East New Britain, West New Britain and New Ireland.[540,541] The work in this thesis facilitated a larger program of collaborative social science TB research in PNG, of which there had been previously very little with the PNG Institute of Medical Research. This collaboration continued and has generated critical knowledge to inform contextually appropriate solutions.[152–155]

Enabling local leadership, collaboration and research capacity building

The SFD TB program's success was fundamentally dependent on strong partnerships and local leadership, under the leadership of the WPHA. Multiple cadres of health workers were trained in high quality models of TB care, who often transferred their skills and knowledge to other settings upon leaving Daru. This includes notable local clinical and public health leaders such as Dr. Stenard Hiasihri and Dr. Maggie Taune, who exemplify the capacity building success.

Although the research was led by international partners, the WHPAs and NTPs ownership of the research agenda created an effective model for knowledge co-production in this program of work and studies conducted in this thesis. The operational research capacity building initiatives (2017 and 2022) through the SORT-IT program, produced 21 PNG-led publications and built local research capacity while generating evidence for program improvement in eight other provinces in PNG (Figure 8.1).[158,458] The eight publications from SFD include operational research on bedaquiline implementation, household contact investigation outcomes, and SWEEP-TB feasibility studies - achievements that other provinces in PNG have not replicated. The 2017 SORT-IT program was held in Daru, under the stewardship of the NTP in collaboration with national research institutions (PNG IMR and the University of PNG). This fulfilled the NDoH's emergency response objective of building Dau as a national TB centre of excellence and resulted in the formation of a national TB research steering committee.

Figure 8.1 SORT-IT research projects undertaken on TB in PNG in 2019 and 2024



Source: Maha et al. [458]

These approaches facilitated knowledge translation into practice and policy, and this experience demonstrates that effective research in such settings requires long-term commitment to partnership building and local capacity strengthening, rather than just technical expertise. It must be noted that these important gains are still fragile, in a system dependent on external funding and prone to shifts in governance models and leadership that undermine sustainability.

Community engagement and partnership

A key innovation was the evolution of community engagement approaches from informing to consulting to involvement and partnership. The establishment of TB survivors as peer counsellors, person-centred care models with input from the affected community (representative group), community health promotion activities and ultimately, formation of the Community Advisory Group built trust and improved outcomes through strengthened service delivery and research implementation.

The program demonstrated that community engagement is not just an adjunct to service delivery but fundamental to successful implementation and research, particularly in disadvantaged communities such as Daru. This was particularly evident in the development of the SWEEP-TB protocol, where community input substantially shaped the intervention design and implementation procedures. The next step on this continuum is co-leadership with community.[542,543]

8.3.2 Global significance

The demonstration that sustained technical assistance and health systems strengthening can lead to TB program improvement and resilience, adoption of innovations and capacity building provides lessons for similar settings globally. The MDR/RR-TB treatment outcomes (>85%) are particularly noteworthy, exceeding global averages and outcomes reported from many better-resourced settings. The COVID-19 impact analysis offers valuable insights into building program resilience through sustained technical assistance - lessons applicable to health system strengthening globally. The mixed-methods approach combining epidemiological analysis, qualitative patient insights, and implementation research provides a replicable framework for comprehensive TB program evaluation in complex settings.

First implementation of a novel community-wide approach, including testing and treating TBI in a high MDR-TB setting

This research generates novel data and approaches for TB prevention in high MDR/RR-TB settings**.** The evaluation of PNG's first community-based contact investigation model demonstrated the feasibility of implementing novel TPT regimens including 3HR and 6Lfx for young child contacts. Most significantly, this led to the development of an innovative community-wide approach to test and treat TB infection through SWEEP-TB - the first implementation of such an approach in a high MDR-TB transmission setting. There have been few other similar contemporary initiatives - in Kiribati and the Marshall Islands the approach used TPT regimens for DS-TB.[544–546]

Identified gaps in current guidelines for implementation of the End TB strategy

This research identified fundamental limitations in current WHO End TB strategy implementation for high MDR/RR-TB transmission settings. The findings challenge the household-based contact investigation paradigm by demonstrating that transmission extends beyond household boundaries. This was supported by the household contact study - 13.2% of contacts had multiple index cases, drug susceptibility concordance between index cases and contacts was only 51.4% for MDR/RR-TB - and the qualitative study. Current guidelines face a critical dilemma: existing tests for TB infection cannot determine the resistance pattern of the infecting strain, and TPT regimen selection is based on index case resistance patterns, with unknown effectiveness when contacts are infected with strains of different resistance profiles.

Innovation in TPT regimen development

To address this dilemma, the development and early implementation of the 6HLfx regimen represents an innovative solution to the challenge of unknown DS/MDR-TB exposure in high-transmission settings.

The rationale for this approach during SWEEP-TB protocol design in 2021 has been subsequently validated by landmark developments in 2024. Two RCTs in 2024 (TB-CHAMP and V-QUIN) demonstrated the effectiveness and safety of 6-months of levofloxacin-based TPT for child and adult MDR-TB contacts.[126,127] The Martinez et al. individual-participant meta-analysis (pre-print publication) showed IPT was 70% effective against incident TB in MDR-TB contacts.[347]

The acceptability and tolerability of 6HLfx, assessed through treatment discontinuation (largely from mild to moderate adverse effects), will be a key finding from SWEEP-TB that will determine the wider application of this regimen. The understanding of TB infection and preventive therapy has evolved significantly during this research program. Ultimately, shorter and safer TPT regimens will be required, including those effective against all types of TB drug-resistance, and TPT regimens should not be developed based on index case drug-susceptibility.

8.4 Future Directions

Building on the foundation of knowledge developed through this thesis, the next frontier requires both application in SFD and broader global research to advance the field. Success will require sustained political commitment, adequate resources, meaningful community engagement and most importantly, the application and rapid uptake of new tools and innovation in high TB burden settings.

8.4.1 Applying and advancing this research in Western Province, PNG

The priorities for the WPHA TB program in SFD are aligned with national and provincial plans to reduce the incidence of TB and strengthen systems. The implementation of SWEEP-TB, which will complete screening at the end of 2025 and follow-up in 2026 is the next step coupled with plans for TB service decentralisation.

Evidence on the acceptability and safety of the novel combination regimen of 6HLfx will be a key advance. Concerns remain about scale-up feasibility due to the resource intensiveness of the model–which will be formally evaluated–in particular, the benefit of

TST prior to TPT. As new tools are developed, scale-up will become more feasible. Economic evaluation, including cost-effectiveness analysis and modelling, was not conducted as part of this thesis but is planned within the ongoing SWEEP-TB evaluation and represents a priority for future research to inform scalability and resource allocation decisions.

A single screening intervention in Daru as implemented in SWEEP-TB may not have a population impact on incidence due to a number of reasons (1) inadequate coverage or uptake of the intervention; (2) a high rate of cyclical migration in and out of Daru, where TB transmission is sustained in mainland areas with limited public health interventions and is seeded back to Daru; and (3) a hyper-endemic transmission setting where transmission is being driven by re-infection and asymptomatic TB that is not being detected.

Priority next steps for SFD

This thesis provides evidence that the overall goal should remain reducing TB incidence, towards TB elimination. It has demonstrated the feasibility of implementing a comprehensive detect-treat-prevent model to operationalise the End TB Strategy in a remote, high-MDR-TB burden setting. Building on SWEEP-TB foundations, three priority areas require immediate attention: enhanced active case finding strategies to detect subclinical TB and reduce transmission; decentralisation of TB services beyond Daru to mainland villages where transmission is sustained; and determining the optimised TPT algorithm to maximise epidemiological impact.

SWEEP-TB data with longitudinal follow-up of groups will be highly informative to address fundamental epidemiological questions:

- Who is at highest risk of progression from TB infection to active disease?
- What is the contribution of asymptomatic TB to ongoing transmission (no TBI or disease, TBI and no disease, TBI completed TPT and TB disease)?
- How do population movement patterns influence transmission dynamics between Daru and mainland villages?

The locally calibrated mathematical model, planned as part of the SWEEP-TB evaluation could guide epidemiological strategy and optimal intervention design. Community co-design and partnership with ongoing acceptability, feasibility and scalability evaluation of any models would be essential.

Frequent, high-intensity interventions will likely be required to reduce TB incidence and should be informed by the results and epidemiological insights from SWEEP-TB. Given the movement and migration of people to and from Daru (temporary, cyclical and permanent), additional data are needed to define a wider geographic zone for an ongoing elimination program. This is likely to be the South and Delta Fly Districts. Mathematical modelling of intervention scenarios would be informative. Priority interventions are likely to be repeat community-wide screening for active TB in Daru, every 12 months, repeated until there is a large (>40% reduction) in case notification. A decision on the optimal TPT strategy would require evaluation of SWEEP-TB. Initially, community-wide screening could focus on active TB detection, without repeat community-wide TPT, given the recent coverage of SWEEP-TB and the implementation challenges of TST administration. However, TPT should be provided to young children, and likely children and young adolescents exposed to TB, given their higher risk of developing TB. Table 8.1 details specific research priorities in the short to medium term in SFD.

Table 8.1 Research priorities for TB in South Fly Distrct, PNG

Research Area	Priorities (2026 – 2030)

Understanding transmission and epidemiology	• The contribution of asymptomatic TB to active TB incidence (being evaluated through SWEEP-TB)
	• Determine who would benefit from TPT (risk of progression to active TB) in Daru through analysis of SWEEP data and prospective follow up
	• Define a geographic zone for a TB elimination intervention
	  ○ Understanding population movement to/from Daru and mainland (evaluated in SWEEP-TB participants)
	  ○ Understanding the prevalence of TB and MDR/RR-TB in the SFD mainland through systematic screening
	• Establish a model to estimate impact of interventions on TB transmission e.g. Serial TBI prevalence studies
	• Ongoing surveillance of TB drug-resistance and molecular epidemiology

Implementation and evaluation	• Repeated intervention in Daru: systematic screening for active and asymptomatic TB +- TPT in Daru • Expanded intervention to develop a model of care (screening, diagnosis and care) for service decentralisation in mainland villages and pathways to health systems integration (e.g. primary care, maternal child health, immunisation) • Studies to evaluate the impact of socio-economic interventions including nutritional support and cash transfers • Modelling epidemiological impact and cost-effectiveness of intervention options and epidemic thresholds
Research approaches	• Embedding community co-design and co-leadership in research design and implementation • Research capacity building initiatives

The scientific foundation established through this thesis and SWEEP-TB implementation provides a unique opportunity to answer fundamental questions about TB elimination strategies in high MDR/RR-TB transmission settings, with implications for similar contexts globally.

8.4.2 Global research priorities

Comprehensive detect-treat-prevent approaches towards ending TB

Understanding the spectrum from TB infection to disease and implementing comprehensive detect-treat-prevent approaches provide systematic frameworks for TB elimination.[12] Recent developments in TB research provide opportunities for enhanced

impact and priority research to address knowledge gaps and new tools will be required to accelerate progress as outlined in Table 8.2. These include research on the contribution of asymptomatic TB to transmission and strategies to optimally detect and treat it, a test for viable TBI and understanding who would benefit most from TPT and shorter pan TB preventive treatment regimens. Significant efforts are being made in develop a new TB vaccine that can interrupt transmission.[110,113,547]

The impact of community-wide TPT and combination prevention

The understanding of TPT's role in interrupting transmission has evolved significantly. From an epidemiological perspective, there is strong evidence that TPT can interrupt transmission when applied at sufficient scale. Historical studies, including Comstock's landmark community-wide trials and other population-based interventions reviewed in Chapter 2, demonstrated measurable reductions in TB incidence through community-wide treatment of TBI, coupled with systematic screening and treatment.[266] However, these approaches were abandoned due to concerns about individual risk-benefit ratios and feasibility and cost in high burden settings.

The ACT-5 study in Vietnam (testing universal TB infection treatment with 3HP) will provide critical evidence for community-wide approaches in moderate transmission settings. [548] This cluster-RCT will evaluate the prevalence of bacteriologically confirmed TB two years after the intervention. It will be conducted in Cau Mau which is not a high MDR/RR-TB transmission setting, however there is a high prevalence of isoniazid resistance.[549] Mathematical modelling consistently suggests that addressing the reservoir of TB infection through prevention interventions is essential for achieving TB elimination, particularly in high-burden settings where transmission extends beyond households.[262,265,546,550]

In high-transmission settings like Daru, where conventional detect-and-treat approaches have proven insufficient to reduce incidence despite high treatment success rates, there is a strong epidemiological rationale for revisiting community-wide prevention strategies. This represents a fundamental shift from individual-focused risk-benefit calculations to population-based strategies where the collective benefit of transmission interruption justifies broader implementation of prevention interventions.[6,174,551]

Table 8.2. Research developments and priorities for ending TB

Category	Recent Developments	Research Priorities
Basic & epidemiological research	• Framework for the spectrum of infection and disease • The recognition of asymptomatic TB's role in transmission [12,161,165] • Clear evidence demonstrating that active case finding for TB reduces prevalence[205,214]	• Biomarkers that identify viable *M. tuberculosis* and distinguish it from disease • Mechanisms and determinants of bacterial latency and progression • Understanding the contribution of asymptomatic TB to transmission • Understanding transmission risk through bioaerosol detection studies
Detection strategies	• Ultra-portable mobile AI-enabled CXR [222,288,552] • Progress toward point-of-care and point of need diagnostics – oral swabs, bioaerosols, multi-disease platforms[553] • Improved understanding of age-related screening algorithms	• Point of care screening tests to identify and distinguish TBI and disease • Diagnostic strategies for disease that detect asymptomatic disease and early TB states • Paediatric diagnostic approaches for bacteriological confirmation and clinical diagnosis • Multi-disease detection and diagnosis
Treatment advances	• Shorter, all-oral regimens for MDR-TB, enable more effective community-based care[77,554] • Person-centred TB care models with socio-economic and nutritional support[97,470] • Improved understanding of post-TB disease and management approaches[555–558]	• Optimal treatment of asymptomatic TB or early TB states • Shorter and better tolerated regimens for all TB • Implementation research on models of decentralised care
Prevention strategies	• Expanded TPT options including shorter rifapentine-based regimens (including children), Lfx for contacts of MDR/RR-TB and the early-stage development of long acting injectables [125–127,261,337,559] • Promising vaccine developments[107,112,547,560,561] • Nutritional support for household contacts[390] • Evaluation of community-wide testing and treatment approaches for TBI[544]	• TB vaccine: pre-exposure or post-exposure • 'Pan-TB TPT' regimens (that cover DS- and MDR-TB exposure) and that are short or long acting • Impact of social interventions • Impact of improving indoor air quality

8.4.3 Conclusion

The HIV epidemic provides a compelling example of how population-based combination prevention approaches can achieve dramatic success through community co-leadership and the application of science that led to effective point-of-care testing for infection, antiretroviral therapy, and pre-exposure prophylaxis.[562] Research was crucial to understand local epidemic dynamics, validate epidemiological impact, and determine optimal implementation strategies for different transmission contexts. To end TB, these lessons from HIV must be systematically applied whilst accounting for TB-specific challenges. These include, understanding airborne transmission that places entire communities at risk, drug resistance that complicates detection, treatment and prevention strategies, and incomplete understanding of pathogenesis—particularly the role of asymptomatic TB and the spectrum from infection to disease.[6,105] These complexities necessitate innovative approaches and not continuing the status quo.

A critical innovation to operationalise the WHO End TB strategy is the expansion comprehensive screening and prevention strategies to interrupt transmission at the population level. Successful implementation requires community partnership and co-leadership,[563] decentralised and community-based interventions[253,254] and data utilisation to inform program adaptation[403] to ensure equitable access to prevention and care. Research should be conducted in parallel with implementation, building local capacity. TB interventions can be used for integration with disease control programs and strengthen primary health service delivery.[545,564,565] Holistic approaches are required to address the structural determinants that drive TB transmission including poverty, nutrition, and housing.[68,71] However, we must not use TB's status as a 'social disease' as an excuse for complacency.[3] Ending TB is the key intervention high-burden settings like Daru can undertake to drive social and economic development.[566–568]

This thesis, through the experience in Daru over 10 years, provides compelling evidence that with community partnership, sustained political commitment, and evidence-based implementation, comprehensive approaches are feasible even in the most challenging settings. The success in virtually eliminating TB as a public health threat in most HICs by the late 20th century demonstrates that ending TB is achievable. The challenge ahead, is to apply comprehensive approaches globally, ensuring that the advances in TB prevention and elimination reach all communities, particularly those in remote and high-transmission settings that have been historically underserved. Ending TB need not remain a distant goal.

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Appendices

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Appendix 1.1: Global strategies for TB control

Strategy (Year)	Objectives	Targets (Year to be achieved)
United Nations Sustainable Development Goals (2016 – 2030)	• Goal 3. Ensure healthy lives and promote well-being for all at all ages • SDG Target 3.3 End the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases	• TB incidence rate: 80% reduction compared with 2015 • Number of TB deaths: 90% reduction compared with 2015 • Proportion of TB affected household facing catastrophic costs due to TB: 0%
WHO End TB Strategy (2016 - 2035)	Pillar 1: Integrated, patient-centered care and prevention • Early diagnosis including universal drug susceptibility testing • Treatment of all people with TB including drug-resistant TB • Collaborative TB/HIV activities and management of comorbidities • Preventive treatment of high-risk persons and vaccination Pillar 2: Bold policies and supportive systems • Political commitment with adequate resources • Engagement of communities, civil society organizations, and providers • Universal health coverage policy and regulatory frameworks • Social protection, poverty alleviation, and addressing determinants Pillar 3: Intensified research and innovation • Discovery, development, and rapid uptake of new	2035 targets • TB incidence rate: 90% reduction compared with 2015 • Number of TB deaths: 95% reduction compared with 2015 • Proportion of TB affected household facing catastrophic costs due to TB: 0% 2025 targets • TB incidence rate: 50% reduction • Number of TB deaths: 75% reduction • TB affected households facing catastrophic costs: 0% • ≥90% Treatment coverage: Number of people that developed TB, and were notified and treated, out of the total estimated number of incident cases in the same year • ≥90% TB treatment success rate: Number of TB patients who were successfully treated out of all notified TB cases • ≥90% Preventive treatment coverage: Number of people living with HIV and children who are contacts of cases who were started on preventive treatment for latent TB infection, out of all those eligible • ≥90% Uptake of new diagnostics and new drugs Number of TB patients who were diagnosed using WHO-recommended rapid tests, out of all TB patients (%). Number of TB patients who were treated with regimens including new

Strategy (Year)	Objectives	Targets (Year to be achieved)
	tools • Research to optimize implementation and impact	TB drugs, out of those eligible for treatment with such drugs (%)
Stop TB Strategy	1. Pursue high-quality DOTS expansion and enhancement 2. Strengthen laboratory networks and implement quality-assured diagnosis 3. Address TB/HIV, MDR-TB, and other challenges 4. Improve health systems 5. Engage all care providers 6. Empower people with TB and communities 7. Enable and promote research	• TB incidence rate: 50% reduction compared with 1990 baseline by 2015 • TB mortality rate: 50% reduction compared with 1990 baseline by 2015
DOTS Strategy	1. Political commitment with increased and sustained financing 2. Case detection through quality-assured bacteriology 3. Standardized treatment with supervision and patient support 4. Effective drug supply and management system 5. Monitoring and evaluation system with impact measurement	• Case detection rate: 70% of infectious (smear positive) TB cases occurring each year • Treatment success rate: 85% cure rate of detected cases
DOTS-Plus	1. Political commitment 2. Coordination 3. Laboratory aspects 4. Treatment strategy 5. Information system and data management.	As above

SDG: Sustainable Development Goal; AIDS: acquired immunodeficiency syndrome; DOTS: directly observed treatment, short-course

Appendix 3.1: Study data definitions

Drug-resistant TB Case Definitions

See Definitions. In addition:

Extensive drug-resistant TB (XDR-TB) defined as (WHO)[1]:

> Prior to 2021: resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to rifampicin resistance.
>
> From 2021: resistance to any fluoroquinolone, plus at least one of either bedaquiline or linezolid, in addition to rifampicin resistance.

TB registration (detection) definitions

TB Case Registration	Definition
Bacteriological confirmed TB case	Where a specimen is positive by smear microscopy, culture or GeneXpert
Clinically diagnosed TB	A case that does not fulfill the criteria for bacteriological confirmation but has been diagnosed by a health worker based on strong clinical evidence and commenced on TB therapy. This includes diagnoses based on x-ray or extrapulmonary TB with laboratory confirmation
Pulmonary tuberculosis (PTB)	Bacteriologically confirmed or clinically diagnosed case of TB involving the lungs or tracheobronchial tree
Extra-pulmonary TB (EPTB)	Bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs.
New	Patients who have never been treated for TB or have taken anti-TB drugs for less than 1 month.
Relapse	Patients that have previously been treated successfully for TB were declared cured or treatment completed at the end of their most recent course of treatment and are now diagnosed with TB (either a true relapse or a new episode of TB caused by reinfection).
Treatment after failure	Patients that have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment.
Treatment after loss to follow up	Patients that have previously been treated for TB (more than one month) and were declared lost to follow-up (more than 2 months) at the end of their most recent course of treatment. (These were previously known as treatment after default patients.)
Other previously treated patients	Patients that have previously been treated for TB but whose outcome after their most recent course of treatment are unknown or undocumented.
Unknown previous treatment patients	Patients with unknown treatment history and that do not fit into any of the above criteria.

[1]World Health Organization. *WHO announces updated definitions of extensively drug-resistant tuberculosis*. 2021. https://www.who.int/news/item/27-01-2021-who-announces-updated-definitions-of-extensively-drug-resistant-tuberculosis

Drug-susceptible TB treatment outcome definitions

Treatment Outcome	Definition
Cure	A smear positive patient who is smear negative in the last month of treatment and on at least one previous follow up examination. Only applicable to patients who were smear positive initially.
Treatment Completed	Patient who has completed treatment but who does not meet the criteria to be classified as a cure or failure.
Treatment Failed	Patient who is smear positive at 5 month or later during treatment. Also applies to smear negative patient who become smear positive at 2 months.
Died	Patient who dies for any reason during the course of treatment.
Lost to follow up	Patient whose treatment was interrupted for two consecutive months of more.
Not Evaluated	A patient who has been transferred to another recording and reporting unit (BMU) and/or for who the treatment outcome is not known.
Treatment Success	Defined as the sum of cured and treatment completed. Mostly used to assess treatment outcome for smear or culture positive patients

MDR/RR-TB Treatment outcome definitions

Outcome	Definition or calculation of indicator
Lost to follow up	Numerator: Number RR-/MDR-TB* patients registered whose treatment was interrupted for two consecutive months or more by the end of their treatment Denominator: Number of RR-/MDR-TB patients who were registered and commenced on MDR-TB treatment
Died	Numerator: Number of RR-/MDR-TB patients registered who died of any cause after treatment initiation Denominator: Number of RR-/MDR-TB patients who were registered and commenced on MDR-TB treatment
Failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: lack of conversion by the end of the intensive phase, or bacteriological reversion in the continuation phase after conversion to negative, or evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or adverse drug reactions (ADRs).
Cure	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment complete	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment success	The sum of cured and treatment completed
Not evaluated	A patient for whom no treatment outcome is assigned. (This includes cases “transferred out” to another treatment unit and whose treatment outcome is unknown)
Baseline or diagnostic culture definition	Any culture sent from 180 days prior to 7 days after RR/MDR-TB treatment start

Appendix 3.2: Programmatic TB interventions, South Fly District, 2011-2022

Programmatic TB Interventions, South Fly District, Western Province, Papua New Guinea, 2011- 2016

Strategic Interventions & Activity Groups	Baseline 2011-2013	Emergency Response 2014-2016
1. Establish a model of patient-centred TB care for diagnosis, treatment and prevention of DS and MDR-TB at Daru		
Diagnosis, Treatment, Care and Prevention	**2011** Model of care in line with DOTS strategy until 2011 when MDR/RR-TB care initiated. Microscopy as initial diagnostic Treatment support for DS-TB with DOT No contract tracing or preventive therapy	**2014** Standardised operating procedures and systems for the clinical and programmatic management of MDR/RR-TB introduced. Strengthened standardised MDR/RR-TB regimen with linezolid and clofazimine and patient monitoring **2015** Xpert MTB/RIF adopted as front-line test for presumptive TB. DS-TB case management team established. Introduction of compassionate use bedaquiline. Standardised patient education and counselling **2016** Child MDR/RR-TB protocols (gastric aspirate, dosing, nutrition) developed. Community treatment sites and supporters for MDR/RR-TB with patient support package (nutrition and transport). Contact Tracing for MDR/RR-TB commenced. Bedaquiline donation program accessed
2. Strengthen health systems building blocks to enable a functional model of TB care		
Governance and coordination	Limited coordination due to complex governance structures - National TB Program for policy, guidelines and supervision. WPHA for community services and DPH for facility care. Cross border clinical collaborative group for TB.	**2014** Formation of Provincial TB Core Group for program management and implementation team meeting. NDoH Emergency Response Taskforce formed for stewardship, government / donor coordination, advocacy and resource mobilisation. Provincial TB physician leads the program. **2015** Joint statement from NDOH and WHO on scale of Daru DR-TB outbreak. Provincial TB strategic plan and SFD implementation plan developed. **2016** Annual implementation planning and review of progress

Strategic Interventions & Activity Groups	Baseline 2011-2013	Emergency Response 2014-2016
Financing	Minimal domestic financing for TB in Western Province Australian Government support from 2012, including transfer of MDR/RR-TB patients and systems strengthening	**2014** Increase in Australian Government funding to engaged technical partner and additional human resources for TB program. **2015** District health services funding for vehicles. Provincial funding for outreach and logistics. **2016** PNG Government emergency funding. Further Australian Government funding for community treatment support and research capacity building program
Human resources, capacity building & technical assistance	Daru TB BMU staff of 7 (including 2 medical officers) supported by a network of volunteer treatment supporters Specialist TB medical officer commenced in 2011 Supervisory visits from NTP WHO monitoring missions	**2014** Remote support from international TB and health systems experts **2015** Daru based international TB experts for clinical and programmatic mentoring and training Infection control plan and committee established. WHO MDR/RR-TB officer at national level. WHO regional green light committee missions in 2015 and 2016.
Information systems, supply chain, & laboratory systems	Paper-based registers and reporting Routine stock outs of consumables and medical supplies Delays in lab turnaround time and results to patients	**2015** Remote connectivity for Xpert. Laboratory protocols, indicators and training established **2016** Electronic medical record system introduced for TB patient care. Electronic stock management tools. National reference lab commenced culture
3**. Improve service utilisation and TB prevention through community engagement**		
Community engagement	Community advocacy and social mobilisation conducted by faith-based organisation	**2015** Formation of community stakeholder alliance in Daru, including community leaders and private sector. **2016** TB patient representatives elected. TB survivors trained as peer counsellors

Strategic Interventions & Activity Groups	Baseline 2011-2013	Emergency Response 2014-2016
4. Program data is utilised for effective action		
Data utilisation and operational research	Routine NTP reporting system with significant gaps in reporting and data utilisation	**2014** Routine reporting, data cleaning and case-level data collection for MDR/RR-TB **2015** Program process indicators for continuous quality improvement established **2016** Research prioritisation. Structured Operational Research Training Initiative (SORT-IT) conducted in Daru
5. Decentralised TB care is established in SFD		
Decentralised care and treatment	TB patients routinely accessing care in Australian Torres Strait until 2012. Medical sea ambulance for patient transport	**2014** District TB Officer commenced decentralised DS-TB care with outreach and follow-up. Retrieval of MDR/RR-TB patients lost to care in Daru and SFD **2015** Community-based treatment support and care in Daru with planning for decentralisation systems for TB monitoring in SFD **2016** Outreach boats (outboard) for patient transport and follow-up in South Fly. Decentralised MDR/RR-TB care commenced in 1 site.

BMU: Basic Management Unit; DOT: directly observed therapy; PEC: patient education and counselling; CAG: community advisory group; SOP: standard operating procedures; PPE: personal protective equipment; IPC: infection prevention and control

Programmatic interventions undertaken for the TB response in South Fly District, Western Province, Papua New Guinea, 2017-2022

Strategic Interventions & Activity Groups	Strengthened systems (Pre-COVID) 2017-2019	COVID 2020-2022
1. Establish a model of patient-centred TB care for diagnosis, treatment and prevention of DS and MDR/RR-TB at Daru		
Diagnosis, Treatment, Care and Prevention	**2017** Introduction of shorter treatment regimens for MDR/RR-TB (9 months, containing injectable agent). Expansion of use of the oral, injectable free long MDR/RR-TB regimen with increasing use of bedaquiline (45% of treatment initiations in 2017 compared with 19% in 2016) Strengthened community treatment sites and support for patient monitoring (side-effects, referral, sputum collection) Psychosocial support with standardised patient education and counselling for DR-TB and DS-TB patients, including referral to family planning, family sexual violence and disability services Child TB initiatives including updated guidelines, training, child-friendly education, counselling Scale up of routine household contact investigation from MDR/RR-TB index cases to include to DS-TB index cases (1384 contacts screened) Routine TB preventive therapy (TPT) for DS-TB for children under 5 (38 initiated TPT) Infection control interventions at DPH including ventilation assessments, triage, respirator fit testing **2018** Systematic screening initiative commenced with chest x-ray with CAD4TB (a single fixed central location on a truck) to detect active TB in Daru residents 10 years and above (led by WHO) Contact investigation expanded to DS-TB index cases **2019** Systematic screening initiative completed early 2019 with good yield (69 additional cases, <1% of those screened), compared with 2.5% in contact screening TB program plans developed for a comprehensive search-treat-prevent model in Daru community (for 2020), ie	**2020** With the onset of the pandemic, the model of care was scaled back to essential services to focus on treatment and care Adaptation of model of care to allow flexible treatment delivery with self-administered treatment for longer periods. New SOPs developed for community-based care (patient triage, sputum transport, infection prevention, care and support) PEC services reduced from March to June, but then resumed as normal for active TB and TPT Facility based TB detection (passive case funding) was constrained due to lack of clinical staff. Reduced attendances to the TB diagnostic centre at DPH was recorded. Active case finding, including household contact investigation and initiation of new patients on TB preventive treatment (TPT) was stopped in March. Plans for population screening were deferred. Household contact investigation resumed in November. No change to treatment regimens COVID-19 training conducted for clinicians, SOPs developed including for IPC, PPE and bidirectional COVID-19 and TB screening and diagnosis COVID-19 planning and response framework developed with WPHA COVID-19 education to TB patients and general community **2021** TPT provision for young child contacts resumed. Weekly clinical reviews decentralised from DPH to community sites. Support to COVID-19 vaccination engagement and delivery program **2022** Return to full TB program activities including routine household contact screening (February), TB diagnostic services and outreach clinics. Xpert XDR introduced at the central public health laboratory (CPHL) BCG coverage improvement from 40.9% (2020), 27.1% (2021) to 66.1% (2022) COVID vaccination education flipchart adopted nationally

Strategic Interventions & Activity Groups	Strengthened systems (Pre-COVID) 2017-2019	COVID 2020-2022
	expanding TPT to older children and adults, given limited yield of active case finding alone. Expanded TPT to young child contacts (under 5 years) of MDR/RR-TB index cases Introduction of new TPT regimens for young child contacts: 3HR and 6Lfx Dedicated peer counsellor for TPT program Xpert Ultra replaced Xpert MTB/RIF BCG assessment following stockouts and low coverage in 2018: BCG coverage in SFD 64% (2017), 21% (2018), 48.4% (2019)	
2. Strengthen health systems building blocks to enable a functional model of TB care		
Governance and coordination	**2017** Regular TB program coordination meetings with WPHO and partners (Burnet, World Vision) Coordination with National Emergency Response Taskforce (ERT) **2018** Partner monitoring framework established **2019** Provincial Health Office (public and community health) and DGH (curative, reporting to NDOH) transitioned to WPHA in September 2019	**2020** New WPHA structures announced and interim executive commenced in Q3 and WPHA building its capacity and operational functions Disruption to routine TB coordination meetings, although weekly partnership meetings held for COVID-19 where TB issues were discussed WPHA TB annual implementation plans not reviewed **2021** Full WPHA executive positions appointed but governance and program functions still impacted . WPHA annual implementation plan reviewed. Ongoing disruptions to some routine coordination meetings. **2022** Return to routine governance meetings and joint planning.
Financing	**2017-18** Australian Government and World Bank/NDOH Emergency TB Project commenced to support systematic screening initiative **2018-19** Additional funding obtained for operational research projects via Australian government research funding, aiming to strengthen data utilisation, expand contact screening and management and molecular epidemiology as operational research (2018-19)	No disruption to TB financing but no increases

Strategic Interventions & Activity Groups	Strengthened systems (Pre-COVID) 2017-2019	COVID 2020-2022
Human resources, capacity building & technical assistance	**2017** Continued partnership model of technical support including international specialists and medical officers through Burnet, supporting care and treatment and community-based screening and prevention Telemedicine case discussions with international experts Training, task-shifting and development and updating of SOPs Contact tracing and TPT teams established without additional resources Provincial TB coordinator (leadership) position remained unfilled with an acting role Gaps in clinical TB roles, filled by short term international advisors **2018** Workforce assessment by WHO Competency framework for TB workforce capacity building developed, following a training needs assessment **2019** TB physician appointed TB human resources review and mapping	**2020** Key roles in the WPHA unfilled due to roles in COVID response Disruption to key TB service delivery clinical and public health roles Demobilisation from PNG of international technical advisers for clinical and public health TB activities (including service delivery support) from 2020 to early 2021. Locally engaged staff remained. Remote support enhanced – included training, monitoring and case discussions / troubleshooting. Significant ongoing gaps in WPHA and DPH clinical TB roles PNG TB clinical fellowship program commenced, rotating clinicians from other provinces to Daru. **2021** WPHA provincial disease control and TB officer appointed **2022** Integration of partner and WPHA roles into endorsed TB program human resources structure Peer counselling program ongoing with child protection, child counselling training, TB/HIV training and exchanges with Commencement of SWEEP-TB (comprehensive community screening and prevention project) in November.
Information systems, supply chain, & laboratory systems	**2017** Introduction of electronic medical records system (EMRS) for DR-TB care and programmatic management in SFD implemented – open source (Bahmni) Review of stock management and procurement systems for community sites and establishment of local storage facilities **2018** Expansion of EMRS to include DS-TB treatment, PEC and contact screening and management **2019** TB data analytics site for WPHA with dashboards developed from EMRS for real-time reporting	**2020** Significant stockouts – PPE, TB drugs (resolved with supplementary orders), Xpert Ultra National TB laboratory for C-DST was not functional and testing not performed TB program office requiring repairs and unable to accommodate staff **2021** Ongoing stockouts of consumables, Xpert Ultra and some MDR/RR-TB drugs (supplementary orders). Temporary disruption to the EMRS Additional TB program office space secured **2022** Implementation of an electronic logistic management information system for non-TB supplies at DPH. Resolution of most stockouts (except cycloserine). Resumption of national TB lab services, including C-DST at CPHL. Xpert XDR available at DPH.

Strategic Interventions & Activity Groups	Strengthened systems (Pre-COVID) 2017-2019	COVID 2020-2022
3. Improve service utilisation and TB prevention through community engagement		
Community engagement	**2017** TB survivors engaged through PEC program Community workshops on community mobilisation and advocacy TB patient and community needs assessment conducted to inform support model **2018** TB patient representative group formed and patient satisfaction surveys conducted **2019** Photovoice activity to document lived experience with TB in Daru, strengthen peer support and build community awareness Community consultations for community-wide screening and prevention conducted, with agreement to form CAG	**2020** First meeting of the CAG for the community-wide screening project (prior to COVID) with plans for community engagement developed Model of community engagement developed for TB applied to COVID-19 Integration of community engagement and education for TB a COVID TB education and counselling Facebook page launched and included COVID-19 information **2021** CAG meetings resumed with terms of reference and self-determined name: *TB Nanito Kopia Kodu Group* (the Voice to Kill TB Forever) **2022** Household engagement, mapping and design and planning for community-wide screening. Patient representative meetings restarted. CAG provided input into screening program design. Community education materials developed for SWEEP-TB (including TPT for adolescents and adults)
4. Program data is utilised for effective action		
Data utilisation and operational research	**2017** EMRS used to establish TB care cascades for program improvement TB research prioritisation and agenda conducted Structured Operational Research Training Initiative (SORT-IT) conducted in Daru Molecular epidemiology of DR-TB in Daru research conducted to inform treatment regimens and public health responses Geographic reconnaissance survey conducted in Daru to quantify households and residents **2018** Socio-behavioural research on case and contact perspectives of TB care conducted 4 SORT-IT studies from SFD completed and presented at PNG medical symposium Quality improvement initiative conducted on sputum	**2020** TB data analytics dashboards developed for program decision makers TB program weekly process indicator reporting commenced to track service utilisation for detection and retention in care and prevention All operational research on hold. Planned SORT-IT course cancelled **2021** Operational research protocol for SWEEP-TB approved by ethics review boards in PNG and Australia Contributed to a national study on the impact of COVID-19 on essential services, including TB **2022** National SORT-IT TB course conducted with 3 projects from WPHA Outbreak investigation conducted for an increase in detection of fluoroquinolone resistant TB

Strategic Interventions & Activity Groups	Strengthened systems (Pre-COVID) 2017-2019	COVID 2020-2022
	collection for patient monitoring (increased from 20% to 82%) Modelling and cost-effectiveness analysis of TB interventions in Daru to inform strategy and planning **2019** TPT operational research commenced including TPT for young child contacts of MDR/RR-TB index cases Publication of 12 operational research articles (4 from SFD) from SORT-IT in journal supplement (Public Health Action)	
5. Decentralised TB care is established in SFD		
Decentralised care and treatment	**2017** Health facility and needs assessments for decentralisation, including survey of DR-TB patient **2018** Decentralisation plans developed to identify 2 priority TB BMUs outside Daru – Mabudawan and Balimo, where trainings were conducted. **2019** Construction of Mabudawan health centre on Torres Strait border. Partner (PNG sustainable development program, SDP) engaged in Balimo to strengthen health centre Aviation clinical outreach visits commence across province via SDP for primary care (not TB specific)	Limited progress on plans for decentralisation of TB services outside Daru and province wide. **2020** Planned visits cancelled. New Mabudawan health centre opened **2021** Education and counselling team conducted training and support visits to decentralised sites, introducing standardised PEC in Balimo. GeneXpert set up in Balimo **2022** Resumption of outreach clinics and training for TB care and support to Balimo. Facility assessment conducted at Mabudawan.

BMU: Basic Management Unit; PEC: patient education and counselling; CAG: community advisory group; SOP: standard operating procedures; PPE: personal protective equipment; IPC: infection prevention and control; C-DST: culture and drug susceptibility testing; CPHL: Central Public Health Laboratory

Appendix 3.3: Publication - Morris et. al. (Public Health Action, 2019

Public Health Action

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International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

PNG SUPPLEMENT

The emergency response to multidrug-resistant tuberculosis in Daru, Western Province, Papua New Guinea, 2014–2017

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Setting: A response to an outbreak of multidrug-resistant tuberculosis (MDR-TB) on Daru Island, South Fly District (SFD), Western Province, Papua New Guinea (PNG) was implemented by a national emergency response taskforce.
Objective: To describe programmatic interventions for TB in SFD and evaluate characteristics of TB case notifications, drug resistance and treatment outcomes.
Design: This was a retrospective cohort study based on routine programmatic data for all patients enrolled on TB treatment at Daru General Hospital from 2014 to 2017.
Results: The response involved high-level political commitment, joint planning, resource mobilisation, community engagement and strengthening TB case detection and treatment. Of 1548 people enrolled on TB treatment, 1208 (78%) had drug-susceptible TB (DS-TB) and 333 (21.5%) had MDR-TB. There was an increase in MDR-TB as a proportion of all TB. Treatment success rates increased over the study period from 55% to 86% for DS-TB, and from 70% to 81% for MDR-TB from 2014 to 2015. The 2014 case notification rate for TB in SFD was 1031/100 000, decreasing to 736/100 000 in 2017.
Conclusion: The outbreak was stabilised through the response from the national and provincial governments and international partners. Additional interventions are needed to decrease the TB burden in Daru.

Multidrug-resistant tuberculosis (MDR-TB, defined as TB resistant to at least isoniazid and rifampicin) is a continuing global public health crisis and a major threat to achieving the World Health Organization's (WHO) target to end the TB epidemic by 2035. Globally, 458 000 new cases of MDR-TB were reported in 2017, with evidence of increasing incidence each year.[1] MDR-TB emerges and spreads in populations served by weak health systems, and transmission continues due to gaps in detection, treatment and prevention. The burden of MDR-TB at the regional, country and sub-national levels is often unknown due to the lack of adequate diagnostics and surveillance, which requires molecular testing or specialised laboratories. As approximately 10% of MDR-TB globally is classified as extensively drug-resistant TB (XDR-TB, i.e., TB resistant to the fluoroquinolones and second-line injectable drugs) and 30% as either fluoroquinolone-resistant or injectable-resistant (pre-XDR-TB), further resistance would be a matter of concern.[2]

Papua New Guinea (PNG) is one of only 14 countries classified by the WHO as having the triple high burden of TB, MDR-TB and TB-human immunodeficiency virus (HIV) co-infection.[1] The first report of MDR-TB in PNG was based on an audit of TB case notifications from clinics in the Australian Torres Strait Islands, bordering the South Fly District (SFD) of Western Province, which showed a dramatic increase in cases among PNG nationals between 1998 and 2002.[3] Subsequent reports from the Torres Strait Islands clinics demonstrated alarming rates of MDR-TB, with evidence of person-to-person spread or primary transmission.[4] In late 2011, Queensland Health (Brisbane, QLD, Australia) commenced the transfer of care of 92 PNG nationals with MDR-TB to the provincial hospital, Daru General Hospital (DGH) in SFD. This was in conjunction with specific financial support from the Australian Government to improve the management of TB in Western Province through the provision of clinical staff, a community engagement partner and the establishment of key infrastructure and service agreements (communications centre, TB ward, drug supply, laboratory support and an outreach boat).[5] Case notifications of MDR-TB in Daru were increasing each year: from 59 cases in 2012, 61 in 2013, to 84 in 2014.[6] In 2013, SFD reported TB case notifications were almost twice as high as the national rate. The treatment success rates for drug-susceptible TB (DS-TB) and MDR-TB in 2013 were respectively 65% and 50%.[7]

Recognising the alarming rates of MDR-TB indicating an outbreak, the emergence of XDR-TB and the need for a concerted programmatic response, the PNG National Department of Health (NDoH) convened an Emergency Response Taskforce for MDR-TB in Western Province and other 'hot spot' provinces, such as the Gulf District and the National Capital District, in August 2014.[8] The response in SFD involved a multi-stakeholder partnership under the leadership of the provincial government and the NDoH.

The aim of the present study was to describe programmatic interventions for TB in SFD during the emergency response, from January 2014 to December 2017, and to evaluate the burden, trends and characteristics of TB case notifications, drug resistance and treatment outcomes during this period.

METHODS

Study design and study population

This is a retrospective cohort study of routine programmatic data from 1 January 2014 to 31 December 2017. The study participants were all registered for TB

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treatment at the Daru TB Basic Management Unit, which provides diagnosis and treatment for people from SFD.

Setting

Western Province is the largest but most sparsely populated province in PNG.[9] The remoteness and limited roads make access to and delivery of health and essential services challenging. Health indicators, where available, are some of the worst in PNG.[10] The Fly River divides the province into three districts, North, Middle and South Fly. Daru Island (population 15 142) is the main residential and service town in SFD (population 59 152) and is notably crowded for an island of approximately 15 km^2 (average household size 7.5).[11] DGH, the provincial referral hospital, is the only facility to provide TB diagnosis and treatment in SFD and is managed under the NDoH. It is a 100-bed provincial referral hospital providing inpatient and outpatient services, including specialist care. It has a large TB department with a 40-bed inpatient unit and ambulatory TB services. The Daru TB Basic Management Unit has management, supervision and monitoring responsibility for SFD. The provincial government leads the TB programme in Western Province with support from the Australian Government through international partners and the National TB Programme (NTP).

Diagnostic methods and treatment model

Two sputum samples were collected from presumptive TB patients where possible, and microscopy was performed at the DGH laboratory using Ziehl–Nielsen staining. If either specimen was smear-positive, one sample would undergo testing with Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) at DGH. From 2016, all presumptive TB patients were tested using Xpert and smear as the initial test. All samples with detected rifampicin resistance were transported by air to the supranational reference laboratory in Brisbane, QLD, Australia, for culture and/or drug susceptibility testing (DST), and from January 2017, the national TB reference laboratory in Port Moresby, PNG, for culture. The methods used for DST are described elsewhere.[6] TB patients were managed according to the national protocols and WHO guidelines, which were revised for MDR-TB in 2016.[12–14]

Data collection, variables and analysis

Programme activities and interventions implemented over the study period were identified from implementation plans and project reports. Data on treatment cohorts were extracted from the programme's electronic medical records system (Bahmni v.0.87; Thoughtworks, Chicago, IL, USA) for MDR-TB and from the TB treatment registers for DS-TB. The data were extracted using automated scripts and imported into Stata v.15 (StataCorp, College Station, TX, USA) for validation, coding and analysis. All treatment episodes for TB were included, unless they were subsequently found not to have TB, in which case they were excluded. The data variables collected included age, sex, place of residence at time of registration, date of TB treatment initiation, TB site, registration category, diagnostic test results, outcomes, culture monitoring and DST results.

The current WHO definitions (2017 PNG guidelines) were used for DS-TB and MDR-TB enrolment and outcomes,[15] with one modification: patients who had a permanent regimen change of at least two anti-tuberculosis drugs due to adverse drug reactions were not strictly classified as treatment failures if the patient was responding to treatment with no evidence of clinical or microbiological failure. In a retrospective review, patients who met this criterion had a change of the injectable to bedaquiline (which became part of the PNG protocol in 2016) or a drug not considered to be core in the regimen (e.g., para-amino salicylic or pyrazinamide). The denominator for case notification rates was taken from the last available PNG national census (2011).[10] For 2014, case-level data on DS-TB patients were not available, and aggregate numbers from routine programme reports to the NTP were used instead. Numbers and proportions were calculated for cases registered and treatment outcomes. For geospatial analysis of disease burden, residence was linked to local-level government areas, and 2015 case notification rates for DS-TB and MDR-TB were used. The data were imported into MapInfo Pro v.16 (Pitney Bowes; Stamford, CT, USA) to generate maps.

Ethics

Ethics approval was provided by the PNG Medical Research Advisory Council, Port Moresby, PNG, and the Alfred Hospital Ethics Committee, Melbourne, VIC, Australia.

RESULTS

Joint strategic and implementation planning was conducted by the provincial TB programme and partners under the stewardship of the provincial and national governments in July 2015. The strategic interventions of the implementation plan, which was aimed to reduce TB transmission, were 1) to establish a model of patient-centred TB care for diagnosis, treatment and prevention of DS-TB and MDR-TB in Daru; 2) to strengthen health systems building blocks, adapted from the WHO framework,[16] to enable a functional model of TB care; 3) to improve service utilisation and TB prevention through community engagement; 4) to use programme data for effective action; and, 5) to establish decentralised TB care at two sites in SFD in 2017. Table 1 shows the programmatic interventions implemented since the emergency response in 2014, grouped according to a framework used for response planning and monitoring.

The case notification rate for all TB in SFD in 2014 was 1031 per 100 000 population and 736/100 000 in 2017. Figure 1 displays the annual number of enrolments for TB treatment for the 2196 people enrolled on TB treatment over the study period. Table 2 shows the demographic and clinical characteristics of the enrolled individuals. Among the 1541 patients from annual cohorts (2015–2017) with complete case-level data available, 1088 (70.6%) were from Daru and 26

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Conflicts of interest: none declared.

TABLE 1 Programmatic interventions undertaken for the TB emergency response in Daru, Western Province, Papua New Guinea, 2014–2017

Strategic interventions	Programme status pre-response (2011–2014)	Emergency response (2014–2017)
Establish a model of patient-centred TB care for diagnosis, treatment and prevention of DS-TB and MDR-TB at Daru		
Technical support	Supervisory visits from NTP WHO monitoring missions	2014: Standardised operating procedures for the clinical and programmatic management of TB introduced. Remote support from international TB and health systems experts 2015: Daru-based international TB experts for clinical and programmatic mentoring and training Infection control plan and committee established WHO MDR-TB officer at national level. WHO regional Green Light Committee missions in 2015 and 2016
Diagnosis, treatment, care and prevention	Model of care in line with DOTS strategy until 2011 when MDR-TB care initiated. Microscopy as frontline test Community-treatment support for DS-TB No contact tracing or preventive therapy	2014: Strengthened standardised MDR-TB regimen with linezolid and clofazimine 2015: Xpert® MTB/RIF adopted as front-line test for presumptive TB. DS-TB case management team established. Introduction of compassionate use bedaquiline. Standardised patient education and counselling 2016: Child MDR-TB protocols (gastric aspirate, dosing, nutrition) developed. Community treatment sites and supporters for MDR-TB with patient support package (nutrition and transport). Contact tracing for MDR-TB commenced. Bedaquiline donation programme accessed 2017: Introduction of shorter treatment regimens for MDR-TB. Scale up of contact tracing with expansion to DS-TB index case. Scale up of preventive therapy for DS-TB for children aged <5 years
Strengthen health systems building blocks to enable a functional model of TB care		
Governance and co-ordination	Limited coordination due to complex governance structures: NTP for policy, guidelines and supervision. PHO for community services and DGH for facility care. Cross-border clinical collaborative group for TB	2014: Formation of Provincial TB Core Group for programme management and implementation team meeting. NDoH Emergency Response Taskforce formed for stewardship, government/donor coordination, advocacy and resource mobilisation. Provincial TB physician leads the programme 2015: Joint statement from NDoH and WHO on scale of Daru DR-TB outbreak. Provincial TB strategic plan and SFD implementation plan developed 2016–2017: Annual implementation planning and review of progress
Financing	Minimal provincial financing for TB. Australian Government support from 2012	2014: Increase in Australian Government funding to engaged technical partner and additional human resources for TB programme 2015: District health services funding for vehicles. Provincial funding for outreach and logistics 2016: PNG Government emergency funding. Further Australian Government funding for community treatment support and research capacity building programme 2017: Australian Government and World Bank/NDOH Emergency TB Project announced
Human resources	Daru TB Unit staff of 7 (including 2 medical officers) supported by a network of volunteer treatment supporters Specialist TB medical officer commenced in 2011	2015: Mobilisation of additional 11 TB health workers—including 2 medical officers, health extension officers, nurses, counsellor, laboratory officer, supply chain officer, data officer 2016: Treatment supporters were re-engaged with remuneration. Further 6 TB health workers recruited for contact tracing and decentralisation. International nursing educators engaged. DGH recruits medical and nursing staff (departmental structures re-established) 2017: Peer counselling team established
Information systems, supply chain and laboratory systems	Paper-based registers and reporting Routine stock outs of consumables and medical supplies Delays in lab turnaround time and results to patients	2015: Remote connectivity for Xpert. Laboratory protocols, indicators and training established 2016: Electronic medical record system introduced for TB patient care. Electronic stock management tools National reference laboratory commenced culture 2017: Electronic medical records system for TB care rolled out at Daru General Hospital
Improve service utilisation and TB prevention through community engagement		
Community engagement	Community advocacy and social mobilisation conducted by faith-based organisation	2015: Formation of community stakeholder alliance in Daru, including community leaders and private sector 2016: TB patient representatives elected. 2017: TB survivors trained as peer counsellors
Programme data is utilised for effective action		
Data utilisation and operational research	Routine NTP reporting	2014: Routine reporting, data cleaning and case-level data collection for MDR-TB 2015: Programme process indicators for continuous quality improvement established 2016: Research prioritisation. Structured Operational Research Training Initiative (SORT-IT) conducted in Daru 2017: Sociobehavioural research conducted and protocol for MDR-TB preventive therapy pilot developed
Decentralised TB care is established in SFD		
Decentralised care and treatment	TB patients routinely accessing care in Australian Torres Strait until 2012. Medical sea ambulance for patient transport	2014: District TB Officer commenced decentralised DS-TB care with outreach and follow-up. Retrieval of MDR-TB patients lost to care 2016: Outreach boats (outboard) for patient transport and follow-up in South Fly. Decentralised MDR-TB care commenced in one site 2017: Health facility assessments for decentralisation

TB = tuberculosis; DS-TB = drug-susceptible TB; MDR-TB = multidrug-resistant TB; NTP = National TB Programme; WHO = World Health Organization; NDoH = National Department of Health; SFD = South Fly District; PNG = Papua New Guinea; PHO = Provincial Health Office; DGH = Daru General Hospital.

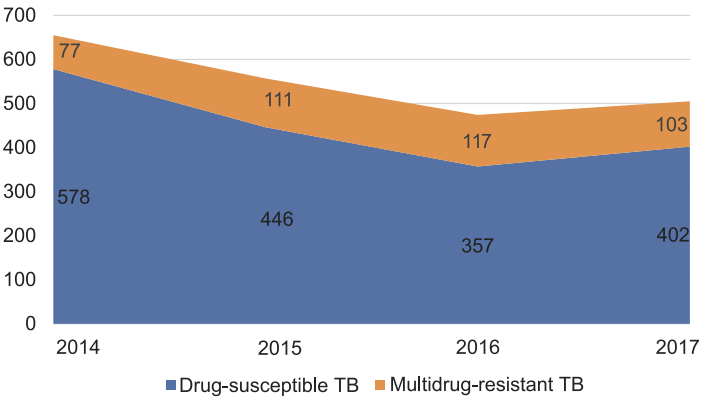

FIGURE 1 TB enrolments at Daru Basic Management Unit, Daru, Papua New Guinea, 2014–2017. TB = tuberculosis.

(1.7%) were HIV-positive. The majority (68.7%) were aged 0–34 years; 18.9% (291/1540) were aged 10–19 years (adolescents, as defined by the WHO). MDR-TB accounted for 413 (18.8%) of all TB cases. Among all MDR-TB patients, 224 (54.2%) were registered as new, indicating that they had not been previously treated for TB. Among the 2017 MDR-TB patients, 81 (78.6%) were registered as new. Thirty-three (8%) of the MDR-TB patients included in the study had pre-XDR- or XDR-TB. The proportion of patients with bacteriological confirmation (smear, Xpert or culture positivity) was 85.4% (286/335) for drug-resistant TB and 50.5% (609/1206) for DS-TB from 2015 to 2017.

The geospatial analyses of 2015 case notification rates by local-level government are shown on the map in Figure 2. Figure 3 shows the treatment outcomes in DS-TB patients enrolled on treatment from 1 January 2014 to 31 July 2017. The treatment success rate increased from 54% in 2014 to 86% in 2017. Figure 4 gives the MDR-TB treatment outcomes for the 2014 and 2015 annual cohorts. The treatment success rate increased from 70% to 81%. The 2016 semester 1 cohort (n = 67) had similar outcomes, with 82% having a successful outcome, 13% having died and 4% who remained in care at the time of analysis. There were no treatment failures or individuals lost to follow-up (LTFU).

DISCUSSION

There is a very high burden of TB in SFD, Western Province. The case notification rates for MDR-TB on Daru Island are some of the highest reported at a subnational level, particularly in a setting with low HIV prevalence.[17] The emergency response resulted in the establishment of a comprehensive programmatic response to TB and improved treatment outcomes for DS-TB and MDR-TB. Case notification trends indicate an overall stabilisation of the TB outbreak, however, with a decrease in DS-TB and increase in MDR-TB.

We report alarming TB case notification rates in Daru of 2021/100 000 for DS-TB and 594/100 000 for MDR-TB in 2015. The available epidemiological data on TB in PNG indicates that there is a TB epidemic nationally with a heterogeneous distribution of drug resistance.[18] A drug resistance survey with a sample of 1182 patients from four provinces reported an MDR-TB rate in 2.7% of new and in 19.1% of previously treated patients.[6] Of the total proportion of MDR-TB patients included in the study, 37% were from the National Capital District and 34% from Daru. Our findings of a geographical clustering of TB in Daru (71%), the high proportion of 'new' MDR-TB cases (82%), along with the high proportion of TB in children (20.1%) and adolescents (18.9%) is consistent with an epidemic driven by person-to-person transmission. A recent molecular epidemiology study has confirmed this to be an outbreak strain of MDR-TB with a long evolutionary history of over 30 years and a unique resistance profile.[19] The study also highlighted the more recent emergence of XDR-TB over 10 years.[19] A major factor likely to be contributing to TB transmission in Daru is overcrowding in homes and in the settlements on the island. This is compounded by the influx of people from surrounding villages in SFD who access services, including those who travel for compensation payments to mining-affected communities and to visit relatives.[10] The contribution of other potential pathogens or host factors (such as diabetes, malnutrition), or transmission through contact outside the household, needs further investigation. It is notable that this outbreak does not appear to be driven by a co-existing HIV epidemic.

Programme reports demonstrate an emergency response focussed on the establishment of a comprehensive programmatic response to TB that has considered the models of care required, as well as the underlying needs to strengthen health systems that underpin the delivery of TB services. Subsequent to this response, increases in the proportion of patients successfully treated for DS-TB and MDR-TB (from 55% to 86% for DS-TB cohorts and from 70% to 82% for MDR-TB cohorts) and, notably, a very low LTFU rate were observed during the study period. Retention in care was achieved through a patient-centred care approach implemented by dedicated case managers (patient monitoring, care coordination), an education and counselling model that trained TB survivors or peers and treatment supporters (Table 1). Ambulatory care was provided at community treatment sites, along with nutritional transportation support as enablers. Community engagement was conducted through community chiefs, patient representatives and health promotion in congregate settings (market, churches and schools). The majority of patients resided on Daru Island or would stay with relatives during the initial period of treatment. The high death rates are of concern and need further investigation, although they may not be comparable to other cohorts where individuals LTFU may have died.

While there were significant challenges at all levels in implementation, the successful elements of the response were the confluence of high-level political commitment; the mobilisation of additional funding and resources to implement the response plan; and collaboration between technical partners and community engagement partners with government stakeholders under the leadership of provincial and hospital authorities. The NDoH, the WHO and partners in PNG called for additional funding in a 'joint statement' on the Daru outbreak.[20,21] There were delays in resource mobilisation and funding for the joint plan developed after the emergency was declared in 2014 (Table 1), prompting advocacy.[20] The response in the study period focused on detection and treatment of TB, as well as the reinforcement of facility and community-based systems with the introduction of diagnostic algorithms and treatment strategies that brought the programme into line with the evolving current global guidelines for MDR-TB. This included initiating patients on MDR-TB treatment using five effective drugs (including linezolid and clofazimine) and introducing bedaquiline into the programme in late 2015.

Case notification trends indicate a stabilisation of the TB outbreak with an observed increase in MDR-TB as a proportion of all TB cases during the study period. Responses to outbreaks of

TABLE 2 Baseline demographic and clinical characteristics of patients treated for TB at Daru Basic Management Unit, Daru, Papua New Guinea, 2014–2017

	Total *n* = 2196 *n* (%)	2014* *n* = 655 *n* (%)	2015 *n* = 561 *n* (%)	2016 *n* = 475 *n* (%)	2017 *n* = 505 *n* (%)
Age group, years					
0–4	117 (7.6)		34 (6.1)	39 (8.2)	44 (8.7)
5–14	192 (12.5)		80 (14.3)	54 (11.4)	58 (11.5)
15–34	749 (48.6)		273 (48.7)	228 (48.0)	248 (49.1)
35–54	380 (24.7)		142 (25.3)	120 (25.3)	118 (23.4)
⩾55	97 (6.3)		27 (4.8)	34 (7.2)	36 (7.1)
Unrecorded	6 (0.4)		5 (0.9)	0	1 (0.2)
Sex					
Male	793 (51.5)		277 (49.4)	251 (52.8)	265 (52.5)
Female	747 (48.5)		283 (50.4)	224 (47.2)	240 (47.5)
Unrecorded	1 (0.1)		1 (0.2)	0	0
Residence					
In Daru	1088 (70.6)		397 (70.8)	334 (70.3)	357 (70.7)
Outside Daru	446 (28.9)		162 (28.9)	140 (29.5)	144 (28.5)
Not recorded	7 (0.5)		2 (0.4)	1 (0.2)	4 (0.8)
HIV status					
Negative	1057 (69.3)		333 (59.9)	310 (66.1)	414 (82.6)
Positive	26 (1.7)		8 (1.4)	5 (1.1)	13 (2.6)
Not recorded	443 (29.0)		215 (38.7)	154 (32.8)	74 (14.8)
Resistance					
DS-TB	1783 (81.2)	578 (88.2)	446 (79.5)	357 (75.2)	402 (79.6)
RR-TB	109 (5.0)	28 (4.3)	19 (3.4)	20 (4.2)	42 (8.3)
MDR-TB	271 (12.3)	47 (7.2)	87 (15.5)	88 (18.5)	49 (9.7)
Pre-XDR-TB	13 (0.6)	0	1 (0.2)	4 (0.8)	8 (1.6)
XDR-TB	20 (0.9)	2 (0.3)	8 (1.4)	6 (1.3)	4 (0.8)
Disease site					
Pulmonary	994 (64.5)		341 (60.8)	302 (63.6)	351 (69.5)
Extrapulmonary	542 (35.2)		220 (39.2)	173 (36.4)	149 (29.5)
Unrecorded	5 (0.3)		0	0	5 (1.0)
Category					
New	1262 (81.9)		412 (73.4)	392 (82.5)	458 (90.7)
Retreatment	239 (15.5)		137 (24.4)	67 (14.1)	35 (6.9)
Other	33 (2.1)		6 (1.1)	16 (3.4)	11 (2.2)
Unrecorded	7 (0.5)		6 (1.1)	0	1 (0.2)
Diagnosis					
Bacteriological	895 (58.1)		233 (41.5)	317 (66.7)	345 (68.3)
Clinical	643 (41.7)		328 (58.5)	158 (33.3)	157 (31.1)
Not recorded	3 (0.2)		0	0	3 (0.6)

*Case-level data were not available for 2014 therefore aggregate reports were used.
TB = tuberculosis; HIV = human immunodeficiency virus; DS-TB = drug-susceptible TB; RR-TB = rifampicin-resistant TB; MDR-TB = multidrug-resistant TB; XDR-TB = extensively drug-resistant TB.

MDR-TB in Micronesia, in Tugela Ferry in South Africa and in industrialised countries have demonstrated that MDR-TB, and even XDR-TB outbreaks, can be rapidly controlled if there is a concerted effort on the part of governments who have high levels of political commitment coupled with support of multiple national and international agencies.[22–24] These responses highlight the possibility of further reducing the TB burden in Daru by using comprehensive approaches that include patient-centred care and community-based case finding and preventive treatment, including for MDR-TB.[25] In each of these outbreaks, responses need to be implemented through fragile health systems that are the antecedent cause. As such, common challenges exist at each level of the response and were also noted in Daru—political commitment from governments, resource mobilisation, the implementation of a comprehensive technical strategy, including research, building local capacity and engaging the affected community.

The strengths of our study included the fact that high-quality data were available from the programme's electronic medical records system, and from regular reports to describe and characterise the response and the TB outcomes. All enrolled patients on TB treatment at DGH over a 4-year period were recorded, with few missing data and enhanced collection of clinical and demographic characteristics. Furthermore, the programme documentation of interventions was comprehensive.

A key limitation was that we could not discern the effect of individual interventions on programme outcomes or determine what had the greatest effect or impact. The trends in case notification are influenced by the case detection strategy used. This was

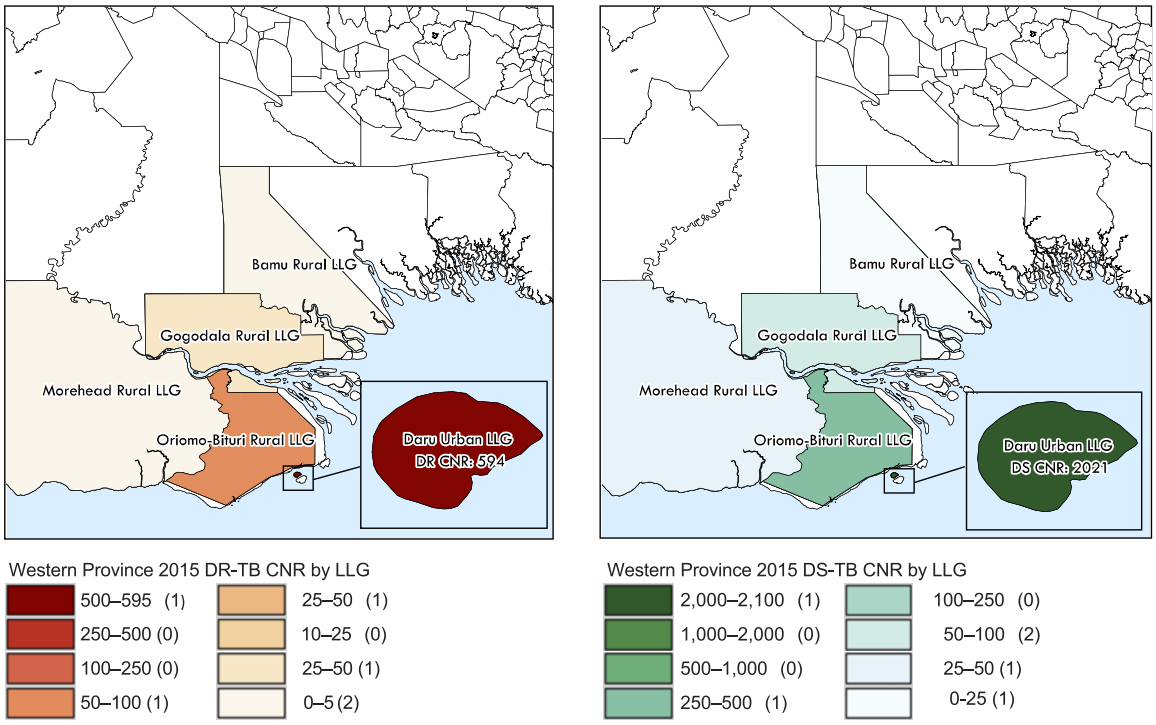

FIGURE 2 Geo-spatial distribution of TB patients enrolled on treatment at Daru Basic Management Unit, Daru, Papua New Guinea, 2015. LLG = local-level government; DR-TB = drug-resistant tuberculosis; CNR = case notification rate; DS-TB = drug-susceptible TB.

consistent since 2016, when Xpert was introduced as the front-line test, which may have led to the proportional increase in MDR-TB. Due to the lack of active case finding for TB outside Daru and limited access to TB services, there may have been an over-reporting bias of residents from Daru.

The MDR-TB outbreak was stabilised through the provision of effective interventions that improved patient care and treatment as a result of concerted efforts from the NDoH, the provincial government and international partners over several years. The developed model of care serves as a template for other provinces in PNG, and has already informed the 2017 national MDR-TB guidelines. While there has been significant progress, the TB burden in Daru and SFD remains extremely high; more ambitious approaches will be required to have a dramatic and swift impact. The situation remains fragile and vulnerable to interruptions in resources or programme delivery. The rates of unfavourable outcomes (death, treatment failure) need to be reduced, and further research to determine who is at risk would be useful. Population screening for active TB commenced on Daru Island in 2018 and the next steps planned by the programme are scaling up a key intervention of household contact tracing and preventive treatment, including high-risk MDR-TB contacts, instituting a capacity building framework to enable transition to the provincial programme and planning for delivery of MDR-TB services outside Daru.

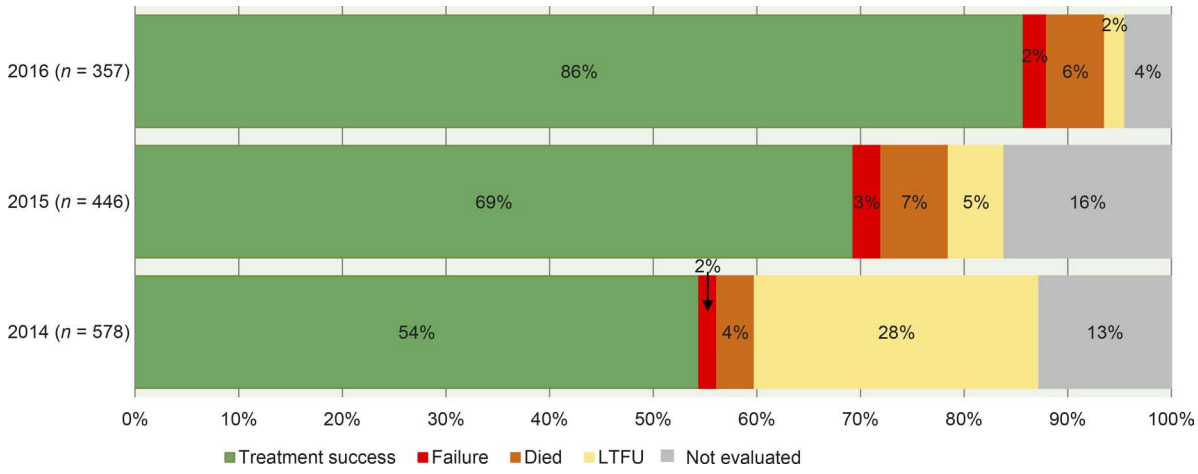

FIGURE 3 Treatment outcomes for drug-susceptible TB patients enrolled on treatment at Daru Basic Management Unit, Daru, Papua New Guinea, 1 January 2014–31 July 2017. LTFU = lost to follow-up; TB = tuberculosis.

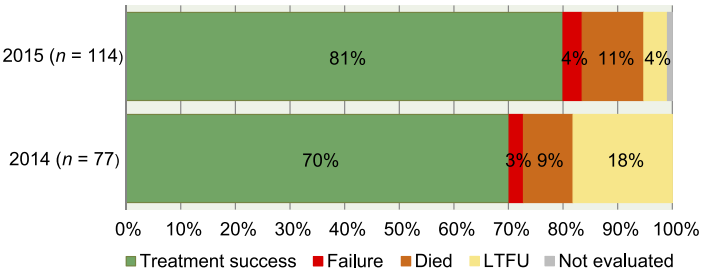

FIGURE 4 Treatment outcomes for multidrug-resistant TB for patients enrolled on treatment at Daru Basic Management Unit, Daru, Papua New Guinea, 1 January 2014–31 December 2015. LTFU = lost to follow-up; TB = tuberculosis.

Additional interventions are needed to reverse the TB outbreak in Daru, decentralise care and build capacity of the health system to sustainably manage the response. With the goal to end the global TB epidemic by 2035, there is an opportunity to promote the rapid uptake of novel tools and intervention strategies to expedite MDR-TB outbreak responses such as new molecular TB diagnostics, shorter, all-oral treatments, scaling up treatment for tuberculous infection and empowering community-driven service models. Research and innovation need to be at the forefront of the TB response and delivered equitably to vulnerable communities and health systems where the needs are greatest.

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Contexte : Reconnaissant une flambée de TB multirésistante (MDR-TB) en Papouasie Nouvelle Guinée (PNG), un groupe de travail d'urgence nationale a mis en œuvre une riposte sur l'ile de Daru, district de South Fly (SFD), province de l'Ouest.

Objectif : Décrire les interventions des programmes relatives à la TB dans le SFD et évaluer les caractéristiques des notifications de cas de TB, la pharmacorésistance et les résultats du traitement.

Schema : Une étude rétrospective de cohorte à partir de données de routine des programmes pour tous les patients enrôlés en traitement de TB à l'hôpital général de Daru de 2014 à 2017.

Resultats : La riposte a impliqué un engagement politique de haut niveau, une planification conjointe, une mobilisation des ressources, un engagement des communautés et un renforcement de la détection des cas de TB et de leur traitement. Sur 1548 personnes enrôlées en traitement de TB, 1208 (78%) ont été des TB pharmacosensibles (DS) et 333 (21,5%) ont été des MDR-TB. Il y a eu une augmentation de la proportion des MDR-TB. Les taux de succès du traitement ont augmenté au long de la période d'étude de 55% à 86% pour la DS-TB et de 70% à 81% pour la MDR-TB en 2014–2015. Le taux de notification des cas de TB dans le SFD en 2014 a été de 1031 par 100 000, diminuant à 736 par 100 000 en 2017.

Conclusion : La stabilisation de la flambée a été obtenue grâce à la riposte des gouvernements national et provinciaux, et des partenaires internationaux. Des interventions supplémentaires pourraient être requises pour réduire le poids de la TB à Daru.

Marco de Referencia: Al reconocer un brote epidémico de tuberculosis multirresistente (MDR-TB) en Papúa Nueva Guinea, el grupo especial de respuesta nacional al brote instauró una respuesta en la Isla Daru, del distrito South Fly, de la Provincia Occidental.
Objetivo: Describir las intervenciones programáticas en materia de TB realizadas en el distrito South Fly y evaluar las características de las notificaciones de casos de tuberculosis, la farmacorresistencia y los desenlaces terapéuticos.
Método: Se llevó a cabo un estudio retrospectivo de cohortes a partir de los datos programáticos corrientes de todos los pacientes inscritos para tratamiento en el Hospital General de la Isla Daru del 2014 al 2017.
Resultados: La respuesta exigió un compromiso político de alto nivel, planeación conjunta, movilización de recursos, participación comunitaria y fortalecimiento de la detección y el tratamiento de los casos de TB. De las 1548 personas inscritas para recibir tratamiento antituberculoso, 1208 presentaban TB farmacosensible (78%) y 333 MDR-TB (21,5%). Se observó un aumento de la proporción de MDR-TB con respecto a todos los casos de TB. Las tasas de éxito terapéutico aumentaron durante el período del estudio de 55% a 86% para la tuberculosis farmacosensible y de 70% a 81% para la MDR-TB, a partir del 2014 y el 2015. La tasa de notificación de casos de TB en distrito South Fly en el 2014 fue 1031 por 100 000 habitantes y se redujo a 736 por 100 000 en el 2017.
Conclusión: Se logró la estabilización del brote epidémico gracias a la respuesta del gobierno nacional y provincial y de los asociados internacionales. Es posible que se precisen nuevas intervenciones a fin de disminuir la carga de morbilidad por TB en Daru.

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Appendix 3.4: Publication: Publication - Bauri et. al. (Public Health Action, 2019)

Public Health Action

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TB IN PNG SERIES

TB programme outcomes in South Fly District, Papua New Guinea, were maintained through COVID-19

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SETTING: An established response to an outbreak of drug-resistant TB (DR-TB) on Daru Island, South Fly District (SFD), Western Province, Papua New Guinea (PNG).

OBJECTIVE: To describe and evaluate the trends in TB case notification disaggregated by demographic and clinical characteristics, programmatic interventions for TB and COVID-19 and treatment outcomes in 2017–2022.

DESIGN: A cohort study of routinely collected programmatic data of all patients registered for TB treatment in SFD comparing pre-COVID (2017–2019) to COVID (2020–2022) periods.

RESULTS: Of the 3,751 TB cases registered, 19.6% had DR-TB, and the case notification rate was 1,792/100,000 for Daru and 623/100,000 for SFD. There was a 29.2% reduction in case notifications from 2019 to 2021, with recovery in 2022. During COVID, the healthcare workforce was adversely impacted, and active TB case-finding was stopped. During COVID, compared to pre-COVID, bacteriological confirmation increased (62.3% to 71.9%), whereas rates of child TB notifications (11.6% to 9.1%), pulmonary TB (60.8% to 57.4%) and DR-TB (20.7% to 18.6%) decreased. High rates of treatment success were maintained for both drug-susceptible (86.5%) and DR-TB (83.6%).

CONCLUSION: Health systems strengthening and community engagement before COVID likely contributed to resilience and mitigated potential impacts on TB in this remote and resource-limited setting. Case notifications remain very high, and additional interventions are needed to interrupt transmission.

TB is a leading cause of morbidity and mortality globally, with an estimated 4,000 deaths each day.[1] Papua New Guinea (PNG) is classified as a high-burden country for both drug-susceptible (DS) and multidrug/rifampicin-resistant TB (MDR/RR-TB) by the WHO. The estimated incidence of TB in PNG in 2022 was 432/100,000 people, and TB mortality in people without HIV was 44/100,000 people.[1] The emergence and transmission of drug-resistant TB (DR-TB) in PNG is a major challenge.[2,3] DR-TB is more complex to diagnose and treat than DS-TB, requiring additional resources, which places stretched health systems under further strain.[4,5]

In the South Fly District (SFD) of Western Province, a significant outbreak of MDR/RR-TB on Daru Island has been the focus of an emergency response since 2014.[4,6,7] We have previously reported on enhanced case detection, improved treatment outcomes, stabilisation of transmission from 2014 to 2017 and initiation of community-based contact investigation and management.[6,8,9] The case notification rate was 736/100,000 in SFD in 2017 and much higher in Daru. Drivers of TB transmission include environmental and socioeconomic factors such as overcrowded settlements, food insecurity and household poverty.[10,11]

The COVID-19 pandemic has caused disruptions to healthcare service delivery, particularly in low and middle-income countries with less resilient health systems.[12,13] The impact on TB services includes reduced case detection and worse treatment outcomes, resulting in unprecedented setbacks to global TB control and almost half a million excess deaths from TB from 2020 to 2022.[1,14] PNG suffered significant disruption to health care and services through workforce impacts, diversion of resources and disrupted systems such as diagnostics and supplies.[12,13] We describe the changes to the TB response before and after the onset of the COVID-19 pandemic and evaluate TB case detection and treatment outcomes in SFD, PNG.

METHODS

Study design and population

A cohort study of routinely collected programmatic data of all people registered with DS and DR-TB in South Fly District, PNG, was conducted from 1 January 2017 to 31 December 2022.

Study setting

Western Province had a population of approximately 315,273 in 2021[15] and is divided into three administrative districts: North Fly District, Middle Fly District and SFD (population: 84,435). The provincial capital is Daru, in SFD, a small and densely populated island with an estimated population of 19,397 in 2021 living predominantly in overcrowded settlements.[15,16] The population fluctuates throughout the year.[11] The remoteness and limited road access make accessing and delivering health and essential services extremely challenging. Daru TB basic management unit (BMU) diagnoses and treats DS and DR-TB for all SFD and parts of Middle Fly District if services are unavailable. It contains the Daru Provincial Hospital (DPH), the provincial referral hospital.

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KEY WORDS
COVID-19; tuberculosis; Papua New Guinea

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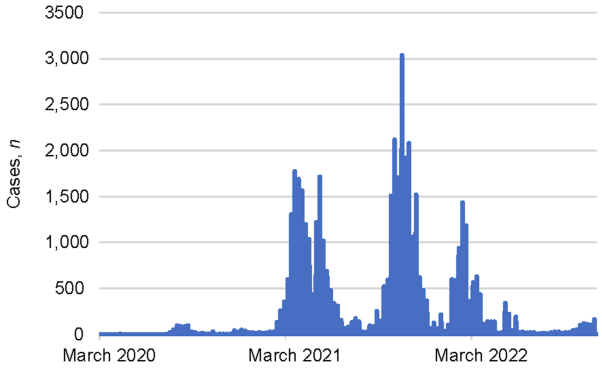

FIGURE 1. COVID-19 notifications in Papua New Guinea, 2020–2022. Source: Based on World Health Organization. Population based on various sources. Geneva, Switzerland: WHO, 2024; adapted by Our World in Data.

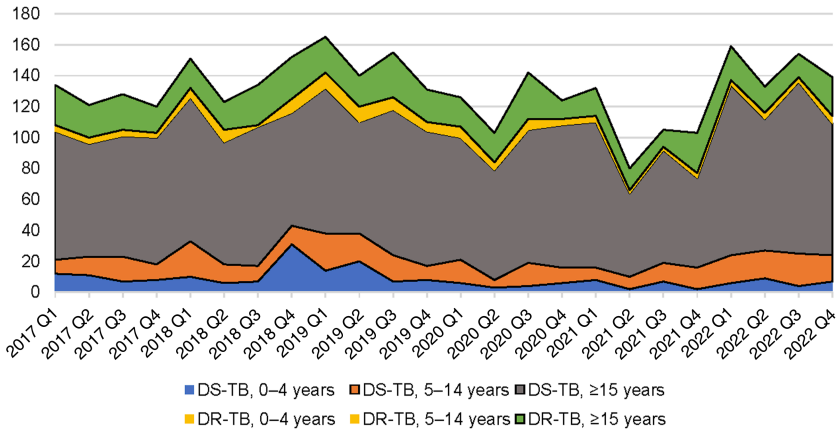

FIGURE 2. TB registrations in South Fly District, PNG, 2017–2022, by age and drug resistance. Q = quarter; DR-TB = drug-resistant TB; DS-TB = drug-susceptible TB; PNG = Papua New Guinea.

TB care and treatment in South Fly District

The Western Provincial Health Authority (WPHA) led the TB response and programme and was supported by implementation partners (Burnet Institute for TB Technical and Implementation Support and Health Systems Strengthening; World Vision for Community Engagement and Care). TB diagnosis is centralised at the DPH TB diagnostic centre, where patients can present themselves, are referred from community sites, or are referred from other hospital units. People with presumptive TB are registered and asked to provide two sputum samples for testing with Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA), the initial test since 2016, in addition to chest radiography (CXR). Paediatric patients who are unable to produce sputum and those with signs or symptoms of extrapulmonary TB may undergo further procedures – gastric aspirate, fine-needle aspiration of lymph nodes – for testing using WHO-recommended molecular rapid diagnostic tests. In 2019, Xpert® Ultra (Cepheid) replaced Xpert MTB/RIF, and in April 2022, Xpert XDR was introduced at the Central Public Health Laboratory (CPHL) in Port Moresby. All samples with MTB detected and rifampicin-resistant are sent to the CPHL for culture and drug susceptibility testing (C-DST). However, C-DST has been unavailable at CPHL since 2020 as the laboratory was not functional. A small number of C-DST samples were sent to the supranational reference laboratory in Australia from early 2022.[13]

DPH was the first site in PNG to systematically introduce the WHO Group A and B MDR-TB drugs, enabling a long all-oral regimen with the corresponding phase-out of injectable agents from 2016.[17] People with TB are managed according to the national TB protocols and WHO guidelines. Previously, regimens for MDR/RR-TB have included four potential standardised regimens:[18] three long (18–24 months) regimens that could consist of an injectable agent or newer TB drugs (bedaquiline, delamanid) and a shorter (9–12 months) regimen that included an injectable agent. Patients with pre- or extensively drug-resistant TB (XDR-TB) were treated with longer regimens.

TB treatment initiation is ambulatory unless patients need admission for medical or social reasons. Treatment delivery is via regular support from

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community health workers and supporters at community treatment sites in Daru. A standard model of care for MDR/RR-TB treatment and care developed in Daru provides patient support with directly observed therapy where possible, as per the national protocol. Since 2016, patient-centred care has been provided for DR-TB in Daru, with patient education and counselling, daily meals, adverse event management and referral.[19] For patients residing outside Daru, treatment is initiated at Daru BMU, but self-administered MDR/RR-TB treatment may be provided for periods for select patients who can be monitored by a family or community treatment supporter and return monthly for clinical review.

COVID-19 in PNG

PNG experienced a small wave of COVID-19 in 2020 and three major waves of reported COVID-19 cases and deaths from 2021 to 2022, as displayed in Figure 1.[12] As of September 2023, when routine reporting stopped, there were over 47,000 confirmed COVID-19 cases and 670 deaths reported.[20] However, this underestimates the actual burden in PNG due to minimal testing, contact tracing and underreporting.[20] Testing rates were persistently low due to barriers such as misinformation, lack of community trust, limited access, and logistic and supply issues.[21]

Health system strain was reported, with hospitals overwhelmed across the second and third waves. A state of emergency was declared on 23 March 2020, involving international border closures, quarantine, a National Pandemic Act, and international resource mobilisation. In the first 100 days, three nationwide lockdowns of up to 2 weeks were instituted where health services only opened to critical and emergency services.[12] After this time, only localised lockdowns were implemented, which were less significant in scale or duration. In August 2020, the 'Niupela Pasin' prevention and mitigation strategy was introduced, emphasising face masks, social distancing and hand hygiene. Isolation and quarantine were generally not enforced, and community uptake of public health measures was generally very low, with variations across the provinces. COVID-19 vaccination commenced in March 2021, but coverage rates were very low; 7.1% of the population received a single dose by the end of 2022.[12] In February 2022, government policy shifted to a reduction in public health measures and testing and international borders were re-opened.

Study definitions

Programmatic interventions, TB notifications, and outcomes were compared between 'pre-COVID' (1 January 2017–31 December 2019) and 'COVID' (1 January 2020–31 December 2022). Annual cohorts were used to note the COVID-19 impacts that commenced in March 2020.

The study definitions used for TB registration and outcomes were per the 2022 WHO definitions[18] and most recent PNG TB guidelines (2017), noting the evolution of DR-TB reporting definitions over time.[22]

Data collection and analysis

At Daru BMU, TB cases are recorded in paper-based programmatic registers and an electronic medical record system (EMR) (Bahmni v.0.87; Thought Works, Chicago, IL, USA). Data were exported from the TB treatment registration dataset and cleaned and analysed using STATA v17 (Stata Corp, College Station, TX, USA). By annual cohort, numbers and proportions were calculated for notified cases and outcomes. Statistical significance between two proportions was tested using standard error.

Annual TB case notification rates were calculated based on population data from 2021 estimates, with residential addresses provided at registration coded to census units.[15] Programmatic activities and interventions were grouped using a conceptual framework based on the objectives in the WPHA TB annual implementation plan – TB model of care (case-finding, treatment and care, prevention), health systems (governance, human resources, financing), community engagement and data utilisation and research. COVID-19 interventions were described in narrative format.

Ethics

This study received ethical approval from the PNG Medical Research Advisory Committee, Port Moresby, PNG.

RESULTS

There were 3,156 people registered for TB in the study period: 1,656 (52.5%) pre-COVID and 1,500 (47.5%) in the COVID period. Figure 2 shows TB registration data by year disaggregated by age and drug resistance. Table 1 displays the clinical and demographic characteristics of people registered with TB from 2017 to 2022 in SFD. There was a 29.2% reduction in case notifications from 2019 to 2021, with recovery in 2022, except for the 0–4-year age group. This disruption was greater in DR-TB (37.0%) than DS-TB (27.0%). Case notification per 100,000 people for SFD was 623 over the entire study period, decreasing by 9.5% from pre-COVID to COVID-19. The case notification rate was 1,792 per 100,000 for Daru residents over the study period.

Among registered people with TB, half (53%) were male, with a median age of 25 years (interquartile range [IQR] 17–40), 20.9% were children (<15 years), 66.1% resided in Daru, and 96.5% were from SFD. Of all people with TB, 66.8% were bacteriologically confirmed (15.5% were under 15 years old), 10.4% were re-treatment, 58.9% were registered as pulmonary TB and 19.6% as DR-TB. HIV infection prevalence was 2.2%; 10% of the cohort had unknown status.

Compared to the pre-COVID period, in the COVID period, there were statistically significant but small increases in residence in Daru and bacteriological confirmation and decreases in TB notifications in young children (0–4 years), pulmonary TB and DR-TB. An increase in RR-TB offset the decrease in MDR-TB in COVID. Pre-XDR and XDR-TB did not change significantly. The overall treatment success rate was 86.5% for DS-TB and 83.6% for DR-TB. Treatment success rates, TB deaths and loss of follow-up did not change significantly during COVID (Figures 3 and 4).

Table 2 describes the programmatic interventions for TB in the pre-COVID and COVID periods. There were impacts on TB services through 2020–2021, with a return to pre-COVID activities in 2022. During the COVID-19 period in SFD, the duration of lockdowns was limited to the initial national period in 2020. Population movement may have been reduced with the reduction in domestic travel and border closures to the Torres Strait (from March 2020 to late 2022). There was a notable and significant impact on the health workforce, including increased absenteeism (isolation and quarantine during waves), diversion of staff to the COVID-19 response, and reduced services. During the COVID period, there was an observed increase in community mask use and significant community engagement and health promotion on prevention measures. Compared with other provinces, there was a concerted vaccination rollout in SFD and the PNG-Australia treaty villages with moderate uptake.

TABLE 1. Clinical and demographic characteristics of people with TB in South Fly District, 2017–2022.

Characteristic	2017–2019 Pre-COVID *n* (%)	2020–2022 COVID *n* (%)	Total *n* (%)
Total people with TB	1,656	1,500	3,156
Median age, years	25	25	25
Age group, years			
0–4	166 (10.0)	79 (5.3)	245 (7.8)
5–14	220 (13.3)	195 (13.0)	415 (13.1)
15–34	735 (44.4)	741 (49.4)	1,476 (46.8)
35–54	390 (23.6)	396 (26.4)	786 (24.9)
≥55	143 (8.6)	89 (5.9)	232 (7.4)
Missing	2 (0.1)	0 (0.0)	2 (0.1)
CNR, /100,000 population			
SFD (all TB)	654	592	623
SFD (DR-TB)	135	109	122
Daru (all TB)	1,806	1,779	1,792
Female sex	795 (48.0)	694 (46.3)	1,489 (47.2)
Primary residence			
Daru	1,051 (63.5)	1,035 (69.0)	2,086 (66.1)
Outside Daru	603 (36.4)	465 (31.0)	1,068 (33.8)
Unknown	2 (0.1)	0 (0.0)	2 (0.1)
South Fly District	1,597 (96.4)	1,448 (96.5)	3,045 (96.5)
Other or Unknown	59 (3.6)	52 (3.5)	111 (3.5)
HIV status			
Negative	1,484 (89.6)	1,390 (92.7)	2,874 (91.1)
Positive	45 (2.7)	31 (2.1)	76 (2.4)
Unknown	127 (7.7)	79 (5.3)	206 (6.5)
Registration			
New	1,469 (88.7)	1,339 (89.3)	2,808 (89.0)
Previously treated	176 (10.6)	152 (10.1)	328 (10.4)
Unknown	11 (0.7)	9 (0.6)	20 (0.6)
Disease site			
Pulmonary	1,075 (64.9)	904 (60.3)	1,979 (62.7)
Extrapulmonary TB	581 (35.1)	595 (39.7)	1,176 (37.3)
Unknown	0 (0.0)	1 (0.1)	1 (0.0)
Diagnosis			
Bacteriologically confirmed	1,026 (62.0)	1,081 (72.1)	2,107 (66.8)
Clinically diagnosed	630 (38.0)	411 (27.4)	1,041 (33.0)
Unknown	0 (0.0)	8 (0.5)	8 (0.3)
Resistance			
Drug-susceptible TB	1,313 (79.3)	1,223 (81.5)	2,536 (80.4)
Drug-resistant TB	343 (20.7)	277 (18.5)	620 (19.6)
Mono/polyresistance	1 (0.1)	1 (0.1)	2 (0.1)
MDR-TB	209 (12.6)	81 (5.4)	290 (9.2)
Rifampicin resistance	96 (5.8)	174 (11.6)	270 (8.6)
Pre-XDR-TB	15 (0.9)	13 (0.9)	28 (0.9)
XDR-TB	14 (0.8)	2 (0.1)	16 (0.5)
Not recorded	8 (0.5)	6 (0.4)	14 (0.4)

CNR = case notification rate; SFD = South Fly District; MDR-TB = multidrug-resistant TB (excluding pre-XDR and XDR-TB); XDR-TB = extensively drug-resistant TB.

DISCUSSION

There are very high TB case notifications in SFD with alarming levels of incident TB in Daru residents (1.8%). TB case detection declined by 29% in 2021 compared to pre-COVID, with recovery in 2022. Despite COVID-related disruptions to TB services, successful TB treatment outcomes were maintained. The interventions and resources directed towards TB and health systems strengthening in Daru and SFD since 2015 have likely contributed to this and may have included - the formation of effective and sustained partnerships and enabling governance mechanisms, the availability of technical assistance during the pandemic, a focus on community engagement, training and development of capacity in the community and health workforce, the implementation of standardised procedures for facility and community-based TB and DR-TB care, and a focus on data management through electronic reporting and data utilisation to inform decision-making.

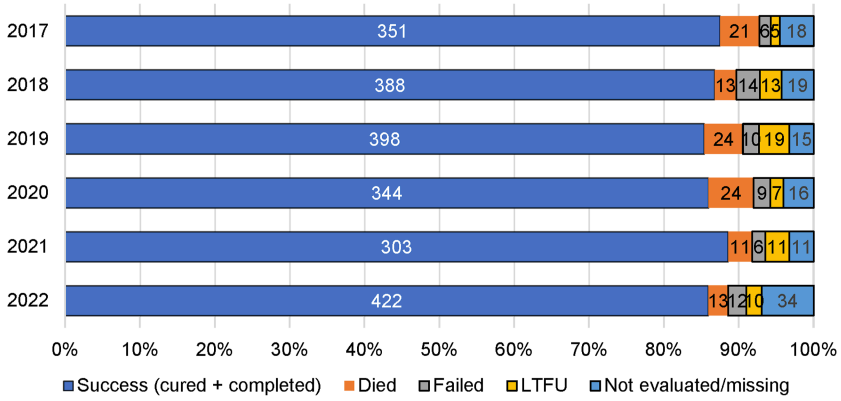

FIGURE 3. Treatment outcomes for drug-susceptible TB from 2017 to 2022 in South Fly District, PNG. LTFU = loss to follow-up; PNG = Papua New Guinea.

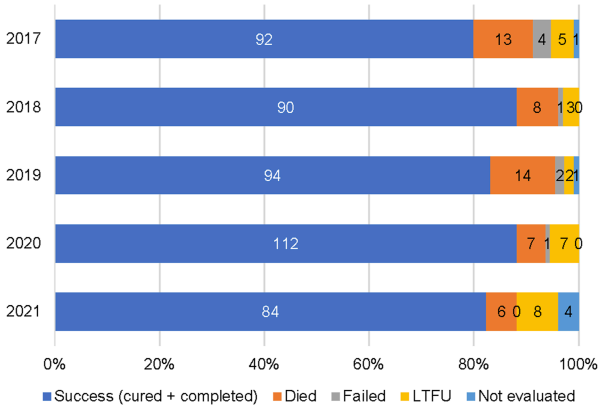

FIGURE 4. Treatment outcomes for drug-resistant TB from 2017 to 2021 in South Fly District, PNG. LTFU = loss to follow-up; PNG = Papua New Guinea.

This study is the first report of TB detection and treatment outcomes during the COVID-19 pandemic in PNG. A strength of the study is the data quality due to the use of the EMR, which was not significantly disrupted during COVID, allowing enhanced TB reporting compared with many similar remote settings. A limitation of the study was that it did not capture COVID-19 surveillance and programmatic activities, nor did it include TB data in SFD, thereby restricting the scope of interpretation. This is a descriptive study with limited information to explain the findings, and therefore, the interpretation is speculative.

The increase in bacteriological confirmation during COVID demonstrates that laboratory diagnostic services remained functional, with a likely reduction in the clinical diagnosis of TB due to human resources shortages. The data from SFD reflect global trends of disruptions to TB services from COVID-19, with an 18% reduction in TB notifications in 2020, partial recovery in 2021 and 2022 levels rebounding to above those in 2019.[1] The Western Pacific had the largest reduction and smallest recovery of all regions. Globally, it was estimated that TB incidence increased by 3.9% from 2020 to 2022, and TB-related deaths increased from 2020 to 2021.[1] This reflects the impact of disruptions to access and provision of TB services during the COVID-19 pandemic that led to more undetected TB and increased transmission.

In SFD, COVID-19-related changes in the health workforce and health system had a major impact on TB services. Active case finding among household contacts was halted, and community access and utilisation of TB diagnostic services were reduced despite the limited duration of lockdowns in SFD. The reduction in TB detection in young children is consistent with observations elsewhere.[23] This may reflect an increased detection gap because of interruption to facility-based services for clinical diagnosis and household screening of child contacts. As TB in young children is a sentinel marker for recent community transmission, it may also indicate less exposure to TB during the COVID period, at least outside of the household setting.

Globally, TB treatment success for MDR/RR-TB dropped to 63% in 2020 and increased to 88% in 2021.[1] That treatment outcomes did not fall in SFD, a remote and resource-limited setting, was likely due to the health systems strengthening activities that had occurred since 2015 and the targeting of the reduced resources on patient care and support – including education, counselling, nutritional support and flexible delivery of care. The peer counselling model that continued during COVID-19 may have been influential – treatment adherence challenges were identified in 43% of 16,234 counselling sessions over the study period.[19,24] People on treatment were supplied TB medications to take home (self-administered treatment), including for DR-TB. The program-initiated process indicators were monitored to track the weekly proportion of patients retained in care, and community health worker teams were engaged in follow-up and support. An examination of lessons from TB and COVID-19 response in Brazil, India and South Africa noted key interventions that can be deployed to address both TB and COVID-19 – behavioural prevention methods, including mask-wearing, screening and contact tracing, digital and mHealth technologies, multi-sectoral engagement and community-led participation.[25]

Operational research from similar low-resource, high TB burden settings has described the impact of the pandemic. In Malawi and Sierra Leone, there was a reduction in TB case detection and maintenance of successful treatment outcomes during COVID-19.[26,27] In other settings such as Brazil, Kazakhstan, Mexico and Zimbabwe, treatment success decreased during the COVID-19 period to early 2021.[28–31] A health systems strengthening and TB quality improvement project in Mimika District, Papua Province, Indonesia demonstrated greater resilience to COVID-19 impacts than reported nationally.[32] The experience in this remote, high-incidence setting was not dissimilar to our experience across the

TABLE 2. Programmatic interventions undertaken as part of the COVID-19 response in SFD, Western Province, PNG.

Strategic interventions	Pre-COVID 2017–2019	COVID 2020–2022
1. Establish a model of patient-centred TB care for diagnosis, treatment and prevention of DS-TB and MDR-TB at Daru		
Diagnosis, treatment, care and prevention	• Scale up of routine household contact investigation from MDR-TB index cases to include DS-TB index cases and TPT for young child contacts (<5 years) • Systematic screening initiative commenced with chest X-ray with CAD4TB to detect active TB in Daru residents ≥10 years old (2018) • BCG assessment following stockouts and low coverage in 2018: BCG coverage in SFD 64% (2017), 21% (2018), 48.4% (2019)	• Model of care was scaled back to essential services to focus on treatment and care, and no active case-finding or TPT in 2020–2021 • Flexible treatment delivery with self-administered treatment • Facility-based TB detection (passive case-finding) was constrained due to a lack of clinical staff • COVID-19 training and bidirectional COVID-19 and TB screening and diagnosis; COVID-19 education to TB patients and general community support to COVID-19 vaccination engagement and delivery programme • BCG coverage improvement from 40.9% (2020) to 27.1% (2021) and 66.1% (2022)
2. Strengthen health systems building blocks to enable a functional model of TB care		
Governance	• Regular TB programme and partner coordination meetings	• Disruption to routine TB coordination meetings and TB annual implementation plans not reviewed in 2020-21
Human resources	• Continued partnership model of international technical support from Burnet: training, development of SOPs, on-the-job mentoring, task-shifting	• Disruption to key TB service delivery clinical and public health roles • Demobilisation from PNG of international technical advisers (2020–2021) and remote support commenced. • PNG TB clinical fellowship program commenced, rotating clinicians from other provinces to Daru (2021)
Information systems, supply chain, and laboratory systems	• Introduction of electronic medical records system (EMRS) for DR-TB care and programmatic management	• Significant stockouts: PPE, TB drugs (resolved with supplementary orders), Xpert Ultra (2020–2021) • National TB laboratory for C-DST was not functional (2020–2021)
3. Improve service utilisation and TB prevention through community engagement		
Community engagement	• TB survivors engaged through the PEC programme • TB patient representative group formed • Community consultations for community-wide screening and prevention conducted, and CAG formed	• CAG and patient representative meetings disrupted until 2022 • Model of community engagement developed for TB applied to COVID-19 • Household engagement for community-wide screening (2022)
4. Programme data are utilised for effective action		
Data utilisation and operational research	• Real-time TB care cascades (EMRS) for programme improvement • Structured Operational Research Training Initiative (SORT-IT) conducted in Daru and course completed	• TB programme weekly process indicator reporting commenced to track service utilisation for detection and retention in care and prevention • All operational research on hold • Planned second SORT-IT delayed until 2022
5. Decentralised TB care is established in SFD		
Decentralise care and treatment	• Health facility and needs assessments for decentralisation, with plans developed • Training conducted at two decentralised sites outside Daru (Mabadawan and Balimo)	• Limited progress on plans for decentralisation of TB services outside Daru and province-wide (2020–2021) • New health centre at Mabudawan opened in 2020

SFD = South Fly District; PNG = Papua New Guinea; DS-TB = drug-susceptible TB; MDR/RR-TB = multidrug and rifampicin-resistant TB; TPT = TB preventive therapy; CAD4TB = Computer-Aided Detection for Tuberculosis; BCG = bacille Calmette-Guèrin; SOP = standard operating procedures; PPE = personal protective equipment; CAG = community advisory group; PEC = patient education and counselling.

border in SFD. There was a drop in annual case notifications by 19%, but treatment outcomes were maintained, and a rapid 'recovery' of detection was noted. Compared with control clinics, a health system strengthening intervention in South African primary health care clinics demonstrated increased TB testing and detection.[33]

There remains an alarming TB notification rate in Daru from 2014 to 2022, with 20% of the burden DR-TB and likely substantial ongoing transmission evidenced by the persistently high rates of case detection since 2014 and a high proportion of TB in children, adolescents and young adults. Most TB notifications are in Daru Island residents, which did not change over time. However, there may be limitations in recording this information (e.g., patients may have cited residence in Daru because they have temporarily relocated to seek health care). Resources, diagnostic services, and community awareness activities have continued focusing on Daru over time, with limited decentralisation; therefore, the burden in wider SFD remains unknown.

Strengthening the TB and health systems in SFD has likely contributed to successfully maintaining TB detection and treatment

outcomes during COVID-19. However, high levels of community transmission remain, and additional interventions are urgently needed to address this. As the health system impacts of the pandemic have declined, the planned community-wide screening and prevention of TB recommenced in Daru in 2023.[9] COVID-19 had a devastating impact in PNG, like many low- and middle-income countries, and has limited progress on TB. The experience in SFD with a long-term (10-year) program of TB technical assistance, coupled with health systems strengthening, has provided resilience to this shock to a degree. There is a need to strengthen health systems as part of TB programs to enhance preparedness for future health threats.[34,35]

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CONTEXTE : Une réponse établie face à une épidémie de TB résistante aux médicaments (DR-TB, pour l'anglais « *drug-resistant TB* ») sur l'île de Daru, dans le district de South Fly (SFD), province occidentale, Papouasie Nouvelle Guinée (PNG).

OBJECTIF : Présenter et évaluer les évolutions concernant la notification des cas de TB, en tenant compte des caractéristiques démographiques et cliniques, ainsi que des interventions programmatiques liées à la TB et au COVID-19, et des résultats thérapeutiques entre 2017 et 2022.

MÉTHODES : Une analyse de cohorte des données programmatiques recueillies systématiquement auprès de tous les patients inscrits pour le traitement de la TB dans le SFD, en comparant les périodes précédant la COVID (2017–2019) à celles durant la COVID (2020–2022).

RÉSULTATS : Parmi les 3 751 cas de TB recensés, 19,6% étaient atteints de DR-TB. Le taux de notification des cas s'élevait à 1 792 pour 100 000 habitants à Daru et à 623 pour 100 000 habitants pour SFD. Entre 2019 et 2021, le nombre de notifications a chuté de 29,2%, avant de connaître une reprise en 2022. Pendant la pandémie de COVID-19, le personnel de santé a été affecté négativement, entraînant l'arrêt de la recherche active des cas de TB. Durant cette période, la confirmation bactériologique a augmenté, passant de 62,3% à 71,9%, tandis que les taux de notification de la TB infantile ont diminué (de 11,6% à 9,1%), tout comme ceux de la TB pulmonaire (de 60,8% à 57,4%) et de la DR-TB (de 20,7% à 18,6%). Les taux de réussite du traitement sont restés élevés pour la TB sensible aux médicaments (86,5%) et pour la DR-TB (83,6%).

CONCLUSION : Le renforcement des systèmes de santé ainsi que l'implication des communautés avant la pandémie de COVID-19 ont sans doute joué un rôle crucial dans la résilience et la réduction des effets potentiels sur la TB dans cette région isolée et à ressources limitées. Les notifications de cas demeurent très élevées, et des mesures supplémentaires sont indispensables pour freiner la transmission.

Public Health Action (PHA) welcomes the submission of articles on all aspects of operational research, including quality improvements, cost-benefit analysis, ethics, equity, access to services and capacity building, with a focus on relevant areas of public health (e.g. infection control, nutrition, TB, HIV, vaccines, smoking, COVID-19, microbial resistance, outbreaks etc).

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Appendix 4.1: COREQ checklist

No. Item	Guide questions/description	Reported in section
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Inter viewer/facilitator	Which author/s conducted the interview or focus group?	4.2.6
2. Credentials	What were the researcher's credentials?	4.2.3
3. Occupation	What was their occupation at the time of the study?	4.2.6
4. Gender	Was the researcher male or female?	4.2.6
5. Experience and training	What experience or training did the researcher have?	4.2.3. 4.2.6
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	4.2.6
7. Participant knowledge of the interviewer	What did the participants know about the researcher?	4.2.6
8. Interviewer characteristics	What characteristics were reported about the inter viewer/facilitator?	4.2.3, 4.2.6
Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study	4.2.7
Participant selection		
10. Sampling	How were participants selected?	4.2.5
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	4.2.5
12. Sample size	How many participants were in the study?	4.2.5
13. Non-participation	How many people refused to participate or dropped out? Reasons?	4.3
Setting		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	4.2.6
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	4.2.6
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	4.3.1
Data collection		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	4.2.6, Appendix 4.2
18. Repeat interviews	Were repeat interviews carried out? If yes, how many?	4.3
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	4.2.6
20. Field notes	Were field notes made during and/or after the inter view or focus group?	4.2.6
21. Duration	What was the duration of the inter views or focus group?	4.3.1

No. Item	Guide questions/description	Reported in section
22. Data saturation	Was data saturation discussed?	4.2.5
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	4.3.2
25. Description of the coding tree	Did authors provide a description of the coding tree?	
26. Derivation of themes	Were themes identified in advance or derived from the data?	4.3.2
27. Software	What software, if applicable, was used to manage the data?	4.3.2
28. Participant checking	Did participants provide feedback on the findings?	4.2.6
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	4.3
30. Data and findings consistent	Was there consistency between the data presented and the findings?	4.3, 4.4
31. Clarity of major themes	Were major themes clearly presented in the findings?	4.4
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	4.4

Source: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. International Journal for Quality in Health Care. 2007. Volume 19, Number 6: pp. 349 – 357

Appendix 4.2: Interview guide for people with TB

SEMI-STRUCTURED INTERVIEW GUIDE FOR PEOPLE WITH TB

After the informed consent is explained and signed, the interview will start with some general questions to make the person feel at ease (informal atmosphere, no sensitive issues). Please remind the participant that you are grateful for their time and that there are no wrong or right answers. This is a time for them to share their story and their knowledge. Reassure them that what they say will be treated in confidence and that their name will not be recorded on any documents to do with the study. Also let them know that they shouldn't feel rushed, worried about time. They are also allowed to skip questions if they feel uncomfortable or can ask for a question to be repeated if it's not clear. Thank them for letting you be privileged to hear their story.

Basic information

Purpose: Understand basic demographic information about the participant and to also get the relaxed to start telling their story and become comfortable with taking and having their voice recorded.

1. Can you tell me a bit about yourself?
   - Ask about: age, marital status, religious affiliation, ethnic group, place of origin.
   - *If a person doesn't know their age, ask then to share a story about an important cultural /historical event in PNG around the time that they were born. Ie. Independence, election of particular prime minister. Or ask questions like what Grade were they in 2000 etc.
2. In PNG we often have children, some of whom are biologically ours and others that aren't but we still care for. Can you tell me about the number and different types of children that you have and care for?
3. Where and with whom do you currently live?
   - How far is that from the nearest:
     - Aid post?
     - Health Centre?
     - Hospital?
4. How are you currently supporting yourself financially? (work, wantoks etc.) What has been you usual occupation, way of making a living? How has your illness affected your ability to earn an income?
5. Before you got sick and were told you had TB, what did you know about TB?
   - Probe for who gets it, how it's transmitted, how you can prevent TB, different types of TB etc.

Experience with TB disease

Purpose: To understand the onset of TB symptoms, what they thought was happening to them, when and why they sought medical care, if they approached traditional healers etc.

1. When and what were the symptoms that you first experienced when you started to get sick with what they now call TB?
   - What did you think was causing those problems?
   - How did the symptoms disrupt your life?
2. How long after the symptoms presented did you first do something about the symptoms?
3. What was it that you did? (traditional medicine, streaming, prayed, antibiotics…)
4. If hadn't been to the clinic - At what point did you then go to the clinic?
5. What made you decide to go to the clinic?
6. Which clinic did you go to and when did you first visit?

7. If you were not told that you had TB. What were you diagnosed as having the first time you went to the clinic? What treatment did they give you?
    - Here we want to understand if a person had to go several times to the clinic before they were suspected or diagnosed with TB
    - Draw out stories of each visit if more than one

TB diagnosis

8. Sometimes people test for TB and are told that they have TB on the same day. For others this is not the case. Sometimes people are in-patients while others are outpatients. Can you share with me your story of when you tested for TB and when you were told had TB
    - How were you tested?
    - When and where were you diagnosed?
    - Who diagnosed you and what did they say about TB? How did that information help you or not?
    - How did you feel when you were told that you had TB?
      Probe for fears, worries, relief, what was helpful etc.
    - How have your thoughts about TB changed since you were diagnosed?

Disclosure of TB

9. Who have you told that you have TB?
   How long after being diagnosed did you tell them?
   What do you say during these conversations?
10. How have they reacted to the information? Probe for the ways in which their treatment/interactions have or have not changed.
11. If haven't disclosed their TB status to anyone, ask why they haven't.
12. Do you ever avoid telling people you are being treated for TB? If so, why and how do you do that?

Treatment for TB

Purpose: To understand experiences, beliefs and behaviours during TB treatment and enablers and barriers to retention in care.

1. Can you tell me about when you started taking TB medicine?
    - When did you start the medicine? – If treatment was delayed after diagnosis probe for why.
    - Why did you start medicine?
2. Can you tell me about how, where and with whom you take your treatment? (DOT/ SAT)
    - What do you like / dislike about this way of taking your treatment?
    - How could it be better?
2. Please describe a typical day when you take your TB medication. Where do you take it?
   Do you have to travel – if so how far and how?
   If you are working, do you need to take time off work or are the drugs brought to you?
3. Some people have a treatment supporter – do you? If No, go to next section. If Yes, Please tell me more about them; Where do you usually see the treatment supporter? How do you feel about the location of the meeting (home visit vs meeting point)? In what ways does it help you?
   How would you change what she/he does?
4. What kind of treatment are you on? What? How often? How much? For how long?
5. How does it feel to be on medicine for TB?
6. What do you like/ dislike about the treatment?
7. What side effect/s have you experienced and how have you coped with them?
8. What were you told about taking treatment everyday?
9. How do you feel the treatment is working?
10. What motivates you to take your treatment?
11. What are the challenges to staying adherent to treatment?
    - What do you do to cope with them?

- What would help you to take treatment?

12. Some times people miss a dose or stop taking medicine for some time. Can you tell me about any times when you have missed a dose or stopped taking your treatment for TB.
    - When?
    - For how long?
13. How often have you missed a dose or stopped treatment?
14. Can you tell me what happened for you to miss your dose or stop treatment?
    - What could help you not to miss it/ interrupt it/ or start it again?
    - Is anybody supporting you to take your treatment? Who? How do they support you?
    - What things or people are making it harder for you to continue or complete your treatment? How? Why?

Engagement and experiences of services

Purpose: To understand experiences, beliefs and attitudes towards TB and health services.

1. Which TB services have you used and what is your experience of them?
    - In-patient Hospital
    - Out-patient Hospital
    - BMU
    - Treatment support
    - Mobile clinic
    - Counselling

Probe:

- What do you like/ dislike about these TB services?
- What challenges or issues have you experienced while accessing any of these services? Please explain.
- In what ways you have been able to manage these challenges/issues?
- In what ways could these services be improved?

2. Some people with TB are seen by a counselor. Have you seen a counselor? What types of things did she/he do with you and how helpful was it? What changed for you after going through counseling?
3. How do you feel about the health staff involved in your care? About the treatment supporters/ CHWs/ HEOs?
4. Could they improve in anything?
5. In what ways are they supportive / not supportive?
6. If you could change anything with the way that they care for you/ approach you, what would it be?
7. Do you have any other recommendations for improving TB care in your area?
8. We are going to conduct this interview with people who live with people with TB . What questions do you think we should ask?

Finish the interview by thanking the participant for their time and sharing their insights. For the last question simply ask them to reflect on what has been shared during their interview and to think about if there was anything important about the experience of TB that we haven't covered and that needs to be understood so others like Doctors etc. can understand what it is like for people in Daru to live with TB.

Appendix 4.3: Participant information and consent forms

PARTICIPANT INFORMATION SHEET

The Social and Cultural Determinants of TB in Daru

People with TB and their contacts: Local beliefs, access to services and treatment experiences in Daru, Western Province, Papua New Guinea

Investigators

Ms Lucy Morris[1], Dr Suman Majumdar[2], Dr Paul Mason[2,3], Dr Angela Kelly-Hanku[4,5], Ms Alice Honjepari[1], Dr Lucia Gonzalez[2], Dr Sonia Madjus[6], Mr Geoff Chan[2], Dr Benny Kombuk[7], Dr William Pomat[4], Dr Paison Dakulala[8], Prof Steve Graham[2].

(1) Provincial Health Office, Western Province (2) Burnet Institute, Melbourne (3) Monash University, Melbourne (4) PNG Institute of Medical Research (5) Kirby Institute, Sydney (6) World Vision International (7) Daru General Hospital, Western Province (8) PNG National Department of Health

You are invited to participate in a study about your health. Please read this information sheet (or ask a friend to read it to you) before you make a decision to take part. Please ask if there is anything that is not clear.

(1) What is the study about?

This study aims to understand your experiences with tuberculosis (TB) disease and how people, particularly you, understand tuberculosis infection. By learning how people living in the community understand and deal with infections such as tuberculosis, we hope to improve how people get diagnosed and treated, how to make treatment more manageable and how to prevent other people becoming infected.

(2) Who is running the project?

The project is being run by health workers and researchers from the Provincial Health Office Western Province, PNG Institute of Medical Research, Daru General Hospital, National Department of Health, Burnet Institute and World Vision International. This study has been approved by the Institutional Review Board of the Papua New Guinea Institute of Medical Research (PNG IMR) and National Depart of Health Medical Research Advisory Committee (MRAC) in Papua New Guinea, as well as ethics boards in Australia.

(3) What do I have to do for the study?

If you want to participate, you will be asked to take part in an interview. The interview will be face to face with the researcher at a time and location that suits you. The interview will involve questions about your basic information, experience with having TB, its treatment and engagement and experience of services. Examples of questions are: "When and what were the symptoms that you first experienced when you started to get sick with what they now call TB? Please describe a typical day when you take your TB medication."

If you are comfortable being interviewed, we would like to ask if we can record the interview. Taking part in the interview does not require recording, so please let us know if you do not feel comfortable being recorded. You can stop the recording at any point during the interview.

(4) Do I have to join or can I withdraw from the study?

Being in this study is completely voluntary. You do not need to participate in this study if you do not want to. If you do choose to participate, you can withdraw at any time.

(5) Will anyone else know that I am part of the study?

Your name and the information collected will be private and only the researchers will have access to your information. During the interview an audio recording will be made. We will use these to make a written record of the interview but will remove all names so that it will not be possible to name you from these

records. All the information collected during interview will remain strictly secret, including any information relating to criminal or illegal activities. Your name will not be made known in the write-up of the results of this study or in any report or publication.

PARTICIPANT INFORMATION SHEET

The Social and Cultural Determinants of TB in Daru

People with TB and their contacts: Local beliefs, access to services and treatment experiences in Daru, Western Province, Papua New Guinea

(6) Will the project benefit me?
Participation will not necessarily directly benefit you other than learning more about tuberculosis, sharing your story and voicing your concerns about existing access to TB screening, diagnosis and treatment. We are trying to understand what it is like living in the community. These results will inform medical staff about local concerns and issues associated with tuberculosis care and prevention. This study will also positively change TB care in Western Province which will benefit Papua New Guineans suffering from TB disease and prevent further spread of Tuberculosis.

(7) **How do I find out the results of the study?**
At the end of the study a community dissemination (information sharing) workshop will be held. A plain language results information sheet will be handed out and the study team will provide one to you. The findings will be presented to the provincial health office and national department of health. It is expected that the study will be made available to the scientific community through publication in academic journals without any of your personal information, such as your name, being published.

(8) What will happen to any recordings once the study is finished?
Recordings will be transcribed and used for analysis. Please tell a researcher if you would not like them to record your interview or if you would like them to stop or get rid of any recordings.

(9) What if I require further information about the project or have a problem?
Once you have read this information sheet, a member of the team will talk to you further and answer any questions you may have. If you would like to know more, please feel free to contact one of our local researchers through the Burnet Institute office at Daru General Hospital: **Lucia Fernandez-Gonzales, Burnet Institute at Daru General Hospital or by email: lucia.gonzalez@burnet.edu.au or telephone: 79825115**

Any person with concerns or complaints about the conduct of the study can contact **Lucy Morris** at the Provincial Health Office (**Phone +67571508697**), Daru, Western Province or by email **lucymorrisdaru@gmail.com**

The Social and Cultural Determinants of TB in Daru

People with TB and their contacts: Local beliefs, access to services and treatment experiences in Daru, Western Province, Papua New Guinea

PARTICIPANT CONSENT FORM

I, ... [PRINT NAME], give consent to my participation in the research project, "People with TB and their contacts: Local beliefs, access to services and treatment experiences in Daru, Western Province, Papua New Guinea."

In giving my consent I acknowledge that:

1. The procedures required for the project and the time involved have been explained to me and any questions I have about the project have been answered to my satisfaction.

2. I have read the Participant Information Statement and have been given the opportunity to discuss the information and my involvement in the project with the researcher/s.

3. I understand that being in this study is completely voluntary – I am not under any obligation to consent.

4. I understand that my involvement is strictly confidential. I understand that any research data gathered from the results of the study may be published however no information about me will be used in any way that is identifiable.

5. I understand that I can withdraw from the study at any time now or in the future.

6. I understand that I can stop the interview at any time if I do not wish to continue, the audio recording will be erased and the information provided will not be included in the study.

7. I understand that I can stop my participation in the focus group at any time if I do not wish to continue; however as it is a group discussion it will not be possible to exclude individual data to that point.

8. I understand that I can obtain results of the study through the end of the study community dissemination (information sharing) workshop and where a plain language information sheet will be handed out.

I or Guardian/Parent on behalf of participant consent to audio-recording:

YES ☐ NO ☐

Name of Participant: _____

Signature of Participant _____ (Date)

Name of Witness/Guardian _____
If consenting on behalf of participant or acknowledging participant has been read and understands the information sheet

Signature of Witness/Guardian _____ (Date)

Appendix 4.4: Characteristics of study participants

Case Number (Pseudonym)	Sex, Age	TB Resistance Profile	Characteristics
Case 1(NTT)	Male, 21	MDR-TB	Pulmonary and extrapulmonary TB, treatment month 13, unemployed, Daru
Case 2 (MBA)	Female, 47	MDR-TB	Pulmonary TB, treatment month 9, market seller, Daru
Case 3 (CBO)	Female, 23	MDR-TB	Pulmonary TB, treatment month 11, unemployed, Daru
Case 4 (EMA)	Male, 38	XDR-TB	Pulmonary TB, treatment month 11, unemployed, Middle fly, relocated for TB
Case 5 (JAN)	Male, 43	MDR-TB	Pulmonary TB, treatment month 6, teacher, South Fly, Port Moresby, relocated for TB
Case 6 (EWV)	Female, 36	XDR-TB	Pulmonary TB, treatment month 6, market seller, South Fly
Case 7 (PBO)	Female, 31	MDR-TB	Pulmonary TB, treatment month 8, community health worker, South Fly
Case 8 (TET)	Male, 61	MDR-TB	Extrapulmonary TB, treatment month 1, retired, South Fly, relocated for TB
Case 9 (ADT)	Male, 72	DS-TB	Pulmonary TB, treatment month 5, market seller, Daru (from South Fly)
Case 10 (STA)	Female, 30	MDR-TB	Pulmonary TB, treatment month 8, fisherperson, Daru (from South Fly)
Case 11 (TGT)	Male, 69	MDR-TB	Pulmonary TB, treatment month 8, market seller, South Fly
Case 12 (JDA)	Male, 49	MDR-TB	Pulmonary TB, treatment month 6, market seller, South Fly, relocated for TB
Case 13 (MNB)	Female, 18	MDR-TB	Pulmonary TB, treatment month 13, pregnancy, Daru
Case 14 (BSN)	Male, 22	MDR-TB	Pulmonary TB, treatment month 19, fisherperson, South Fly
Case 15 (DAN)	Male, 20	MDR-TB	Pulmonary TB, treatment month16, fisherperson, Daru
Case 16 (TSN)	Male, 45	MDR-TB	Pulmonary TB, treatment month 18, South Fly, relocated for TB
Case 17 (SUB)	Female, 28	DS-TB	Pulmonary TB, treatment month 3, South Fly
Case 18 IDS)	Female, 51	DS-TB	Extrapulmonary TB, treatment month 3, market seller, Daru
Case 19 (HKS)	Female, 37	DS-TB	Pulmonary TB, treatment month 2, Daru (lives in Indonesia), relocated for TB
Case 20 (SSW)	Female, 28	DS-TB	Pulmonary TB, treatment month 4, two children on TPT, South Fly, relocated for TB

DS-TB: Drug-susceptible TB; MDRTB: multidrug- resistant TB; XDR-TB: extensively drug-resistant TB

Appendix 5.1: Study tools and data collection forms

DARU HOUSEHOLD TB MAPPING TOOL v.12

Date HMT initiated: _____ **DART site:** _____ **Name of IC:** _____

DOB: ____/____/____or age:_____ **IC's Sex:** ☐ M ☐ F **Address:** _____

Phone Number: _____ **Treatment supporter:** _____

Other family members with TB: _____

Type of TB: ☐ PTB ☐ EPTB: **Pattern of resistance for IC:** ☐ DS-TB ☐ MDR-TB ☐ pre XDR-TB ☐ XDR-TB

IC smear result: ☐neg ☐1+ ☐2+ ☐3+ ☐ scanty ☐ not done **IC HIV status:** ☐ HIV positive ☐ HIV negative

Verbal consent obtained for home visit: ☐ Yes ☐ No **Date home visits:** ☐ 1st_____ ☐ 2nd_____

TB Number:	
Household ID:	
Summary (Coordinator to fill)	
Date household closed: ____/____/____.	
Total number of contacts screened	
Total number of contacts screening positive	
Total number of contacts with sputum collected	
Total number of contacts referred to TBDC	

Children 5 Years and under

Name and Surname	Age	DOB DD/MM/YY	Sex M/F	Relation to IC	Sleep Location B/R/O	WEIGHT kg	MUAC cm	TB symptoms C,F,NS,W, EPTB	TB Screening + / -	TST Y/ N Result (cm)	Referred TBDC /DART site? Mark **T** or **D**	Date seen	Sputum collected Date	Xpert results		CXR TB Y/N Date	TB treatment Start Date	PT Start Date	Remarks
														MTB Detec/ ND	Rif Resist Detec/ ND/ Indet				
1.																			
2.																			
3.																			
4.																			
5.																			
6.																			
7.																			
8.																			
9.																			
10.																			
11.																			
12.																			

Contact definition: any person who has slept in the same house as the index case in the last 3 days

Key	**TB symptoms**	**C =** Cough more than 2 weeks, **F =** Fever more than 2 weeks, **NS =** Night sweats more than 2 weeks, **W =** Weight loss/Failure to thrive, **EPTB =** any symptom of EPTB (marked LN, spine deformity)	
Relationship to IC	**BIL**= Brother-in-law, **SIL**= Sister-in-law	**Sleep location in relation to IC**	**B=** Same bed, **R=** Same room, **O=** Other room
TB treatment	Already on treatment mark **Y**, enter date treatment commenced	**PT = preventive therapy**	Enter date commenced

Children >5 years and adults

Name and Surname	Age	Sex M/F	Relation to IC	Sleep Location B/R/O	WEIGHT kg	TB symptoms C,F,NS,W, EPTB	TB Screening + / -	TST Y/ N Result (cm)	Referred to TBDC Y_Date seen	Sputum collected Date	Xpert results		CXR Date	TB treatment Start Date	Remarks
											MTB Detec/ ND	Rif Resist Detec/ ND/ Indet			
1.															
2.															
3.															
4.															
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23.															
24.															

Household notes:

Preventive Therapy Patient Enrolment & Monitoring Form

Participant study number:_____ **PT Register Number: _____**

Name: _____

DART site: _____ **Regimen (circle):** **TST Result:** mm **Date:**

Age: _____ **Sex: _____** **3RH** **6LFX**

On treatment	Month	Date	Adverse Effects (record on back)		TB Symptoms		Weigh t (kg)	PT Dose	Referrals	Tablets in/out	Next visit
	0		Y	N	Y	N				--/	
	D14		Y	N	Y	N				/	
	1		Y	N	Y	N				/	
	2		Y	N	Y	N				/	
	3		Y	N	Y	N				/	
	4		Y	N	Y	N				/	
	5		Y	N	Y	N				/	
	6		Y	N	Y	N				/--	

Post treatment Visit number	Months post completion	Date	TB Symptoms		Wt
	+3		Y	N	
	+6		Y	N	
	+12		Y	N	
	+15		Y	N	
	+18		Y	N	

Treatment Outcome	
Date	
Complete	
Failed (developed TB)	
Died	
Not complete	

Reason for non-completion	Remarks
1. Patient choice (a) adverse effect (b) social barrier (c) left Daru	
2. Clinical decision (a) adverse effect (b)new exclusion criteria 3. Other	

Adverse Events Monitoring

Adverse event	Date started	Date ended *or* ongoing	Related to PT?	Action taken	Severity Grade	Outcome
	__/__/__	__/__/__ ☐ ongoing	☐ Yes ☐ No ☐ Unclear	☐ Continued drug ☐ Stopped drug	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐Not resolved ☐Resolved without sequelae ☐ Resolved with sequelae
	__/__/__	__/__/__ ☐ ongoing	☐ Yes ☐ No ☐ Unclear	☐ Continued drug ☐ Stopped drug	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐Not resolved ☐Resolved without sequelae ☐ Resolved with sequelae
	__/__/__	__/__/__ ☐ ongoing	☐ Yes ☐ No ☐ Unclear	☐ Continued drug ☐ Stopped drug	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐Not resolved ☐Resolved without sequelae ☐ Resolved with sequelae
	__/__/__	__/__/__ ☐ ongoing	☐ Yes ☐ No ☐ Unclear	☐ Continued drug ☐ Stopped drug	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐Not resolved ☐Resolved without sequelae ☐ Resolved with sequelae
	__/__/__	__/__/__ ☐ ongoing	☐ Yes ☐ No ☐ Unclear	☐ Continued drug ☐ Stopped drug	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐Not resolved ☐Resolved without sequelae ☐ Resolved with sequelae
	__/__/__	__/__/__ ☐ ongoing	☐ Yes ☐ No ☐ Unclear	☐ Continued drug ☐ Stopped drug	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐Not resolved ☐Resolved without sequelae ☐ Resolved with sequelae

Participant no: __ __ __ __ __

Preventive Therapy: Treatment Card

DART site: **Registration Number:** **Name:** **Age:** **Sex:**

Treatment regimen (circle): Isoniazid/Rifampicin 3 months Levofloxacin 6 months

	Date	Wt	Dose	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Ne vis
Month 0				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Month 1				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Month 2				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Month 3				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Month 4				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Month 5				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Month 6				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	

Date outcome: **Outcome:** Completed Developed TB Died Not complete

Participant no: __ __ __ __ __

Preventive Therapy: Treatment Card

DART site: **Registration Number:** **Name:** **Age:** **Sex:**

Treatment regimen (circle): Isoniazid/Rifampicin 3 months Levofloxacin 6 months

	Date	Wt	Dose	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Ne vis
Month 0				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Month 1				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Month 2				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Month 3				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Month 4				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Month 5				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Month 6				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	

Date outcome: **Outcome:** Completed Developed TB Died Not complete N

Treatment (circle number of tablets needed)

Half

1

2

3

Tablets once per day – every day

Pyridoxine (for DS contacts only – cross out if DR contact)

Half 1

Every second day

If you have any problems with giving the medicine, go to the DART site

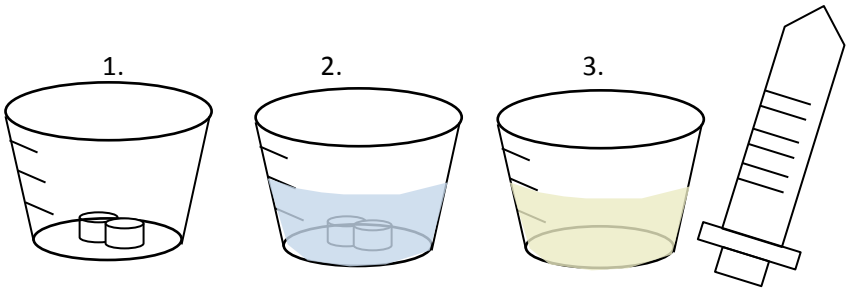
If the child vomits within 1 hour of taking the medicine, you can give the dose again

Try to give medicine at the same time every day

If the child is unwell, go to the DART site or DGH

1. If your child cannot swallow the tablet, put the required amount of tablets into the medicine cup.
2. Add a small amount of clean water.
3. Mix until all dissolved.

The child can drink from the medicine cup, or if a small baby, give using the syringe – squirt it into the baby's cheek



Treatment (circle number of tablets needed)

Half

1

2

3

Tablets once per day – every day

Pyridoxine (for DS contacts only – cross out if DR contact)

Half 1

Every second day

If you have any problems with giving the medicine, go to the DART site

If the child vomits within 1 hour of taking the medicine, you can give the dose again

Try to give medicine at the same time every day

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1. If your child cannot swallow the tablet, put the required amount of tablets into the medicine cup.
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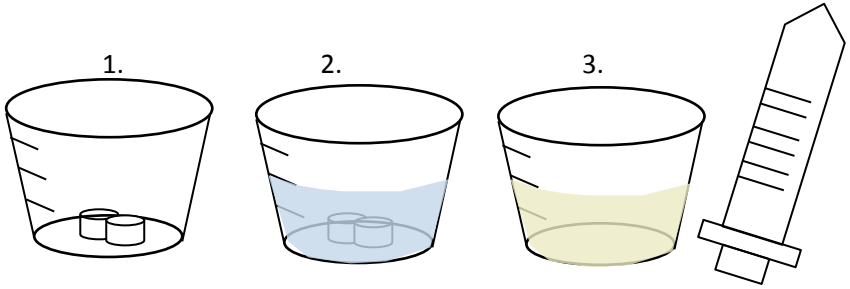
3. Mix until all dissolved.

The child can drink from the medicine cup, or if a small baby, give using the syringe – squirt it into the baby's cheek



Appendix 5.2: Participant information and consent forms

ESCAPE-TB: Enhanced screening and preventive therapy for TB in Daru, South Fly District, Papua New Guinea

PARTICIPANT CONSENT FORM

I, ... [PRINT NAME OF PARTICIPANT], give consent to my participation in the research project, "Enhanced screening and preventive therapy for TB in Daru, South Fly District, Papua New Guinea"

In giving my consent I acknowledge that:

1. The procedures required for the project and any possible risks have been explained to me, and any questions I have about the project have been answered to my satisfaction.
2. I have read the Participant Information Statement, or have had it read to me, and have been given the opportunity to discuss the information and my/my child's involvement in the project with the researcher/s.
3. I understand that being in this study is completely voluntary – I am/my child is not under any obligation to consent.
4. I understand that my/my child's involvement is strictly confidential. I understand that any research data gathered from the results of the study may be published however no information about me/my child will be used in any way that is identifiable.
5. I understand that I/my child can withdraw from the study at any time now or in the future.
6. I understand that if I/my child has commenced treatment for latent TB infection, and withdraw from participation in the study, I/my child will be required to stop taking the treatment. I understand that if I/my child stops taking the treatment I/my child may be at increased risk of developing TB disease as compared to staying on the treatment. I also understand that if I/my child withdraws for the research project that I/my child can still access standard care and treatment as part of the TB program in Daru.
7. If I withdraw my consent, I understand that any information collected until the point I/my child leaves the study may be used for this research project.
8. I understand that I can obtain results of the study at the end of the study community information workshop, where a plain language information sheet will be handed out.

I or Guardian/Parent on behalf of participant consent to participate:

YES NO

Name of Participant _____
Signature of Participant _____ (Date)/____/____

If participant is child, or unable to sign:
Name of Parent/Guardian _____
Signature of Parent/Guardian _____ (Date)/____/____

If consenting on behalf of participant, I acknowledge participant has been read and understands the information sheet.

Name of witness _____
Signature of witness _____(Date) ____/____/____

PARTICIPANT INFORMATION STATEMENT

ESCAPE-TB: Enhanced screening and preventive therapy for TB in Daru, South Fly District, Papua New Guinea

You are invited to take part in this research project TB screening and treatment in in Daru. Please read this information sheet (or ask a friend to read it to you) before you make a decision to take part. Please ask if there is anything that is not clear.

(1) What is this study about?

The project will help to find treatments for sleeping TB in household contacts of TB patients that are effective and well tolerated. The project is being conducted in Daru, Western Province, Papua New Guinea. About 2000 people will take part in this study, and around 200 of these people will be given medication to treat sleeping TB infection.

(2) Who is running the project?

The study is being conducted by researchers from the Western Province Provincial Health Authority, Daru General Hospital, World Vision International PNG and Burnet Institute.

(3) Why is the study being done?

TB is a disease caused by a germ that spreads through the air when people cough or sneeze. It can affect any part of the body, but mainly the lungs. TB affects thousands of people in Papua New Guinea every year. Because it is spread through the air, it is common for people living in the same house as a TB patient to also have TB. Not every person exposed to TB germs gets sick with TB, but many people develop a sleeping TB infection. People with sleeping TB will not have any symptoms of TB and are not able to pass it on to others, but it may grow into active TB disease and make them very sick and able to pass it to others. Sleeping TB is especially likely to turn into active TB disease in young children, or who people are living with Human Immunodeficiency Virus (HIV), as their immune systems that protect them from disease are not as strong. It is possible to treat the sleeping TB before it turns into TB disease and makes people sick. Treatment for sleeping TB in children under 5 who are contacts of a DS-TB case, has recently started in Daru, and currently requires 6 months of daily treatment with an oral medicine. This study aims to treat contacts of DS-TB cases (who are under 5 or HIV positive) with treatment for 3 months- a shorter treatment is expected to be easier for people to take, and can mean fewer side effects as the medicines are taken for a shorter time. Currently there are no guidelines in PNG about the treatment of sleeping TB infection in contacts of MDR-TB cases, but there are a number of studies in other countries showing that the medicine Levofloxacin is effective. This study aims to treat contacts of MDR-TB cases (who are under 5 or HIV positive) with Levofloxacin for 6 months.

(4) What do I have to do for the study?

Screening

Trained health workers will visit your home and ask some questions about your health. They will also ask you about where you sleep in the house, to help work out your risk of getting TB. You will be weighed, and for children under 5, an arm measurement will be taken to check for malnutrition. If you have any symptoms of TB disease, you will be asked to give a sputum sample coughed up from your lungs, and you will be asked to come to Daru General Hospital to have an Xray of your lungs and be reviewed by a doctor or HEO.

TB skin test

If you do not have any symptoms of TB disease, you will undergo testing for sleeping TB infection. The test (called TST) involves a small injection of a solution into the skin of your arm. The injection will cause a small reaction or small bump in the skin. After 48-72 hours, a

healthcare worker will visit to check the reaction and measure it. Depending on the size of the reaction, you will be confirmed to be either positive for sleeping TB infection or not. After a few days the reaction will go away by itself.

HIV testing
If someone living in your house, or a close family member has Human Immunodeficiency Virus (HIV) you will be offered testing for HIV. People living with HIV are more likely to progress quickly from sleeping TB infection to active TB disease. HIV testing is done by a trained HIV tester, and involves a collecting a small amount of blood from your fingertip. If you are found to have HIV, you will be reviewed by the doctor and may need to have further tests and start medication.

Treatment for sleeping (eligible contacts)
If you are under 5 years old, or have HIV, and do not have any TB symptoms, you may be offered treatment for your 'sleeping' TB infection. If you are a contact of a DS-TB case, you will be offered 3 months of treatment with Rifampicin and Isoniazid. It involves taking medicine once a day for 3 months. If you are a contact of an MDR-TB case, you will be offered 6 months of treatment with Levofloxacin, taken once every day.

If you or your child is starts treatment for sleeping TB infection, you will be shown how to prepare the medicine. You will see the HEO at the DART site every month while taking the treatment. At these visits, you (or your child) will be weighed, checked for any side effects, and checked for any symptoms of TB disease. You will be given the next months' worth of treatment. A counsellor may see you if you are having any problems with the medicine. You will be seen monthly in the DART site until you are completed treatment. Once you have completed treatment, you will see the HEO in the DART site every three months until 1 year after you first started the treatment.

If you did not start treatment for sleeping TB, you will be checked every 6 months for symptoms of TB disease.

(5) What are the risks in participating?
If you are started on treatment for sleeping TB infection, there is a small chance that you may have side effects. For contacts who take Rifampicin and Isoniazid, it is possible you may experience:

- Allergy to the medicine
- Orange staining of tears or urine
- Stomach upset
- Numbness or pain in hands and feet
- Liver problems
- Changes in your full blood count test

You will also be given Vitamin B6 tablets to take while you are on treatment, to reduce the chance of numbness or pain in hands and feet (peripheral neuropathy)

For contacts who take Levofloxacin, it possible you may experience:

- Allergy to the medicine
- Stomach upset
- Headache, dizziness, trouble sleeping, tremors

A health worker will provide more education on side effects when starting the medicine. If side effects become bad, the doctor may stop the medicine, and report it to the ethics council that oversees the safety of this study. If you develop any symptoms in between appointments you should come to the DART site, or the hospital.

If you have the test for sleeping TB, you may feel a small amount of pain from the injection. It is possible that you may experience a skin rash or bruising. Very rarely a scar may form at the site. If these or any other symptoms occur please let the study team know.

(6) What are the benefits in taking part in the study?

If you are eligible for treatment for 'sleeping' TB it means you will have a lower risk of getting sick from TB. The project will reduce suffering and prevent death from TB in young children and people living with HIV. Even for people who do not take the treatment, there is a benefit as the skin test will show if you have 'sleeping' TB infection – you will be educated on signs and symptoms of TB disease and you will be encouraged to attend the hospital sooner if you develop any signs and symptoms. It is expected that the number of cases of TB disease in Daru will be reduced in future because of this study

(7) Do I have to take part in the study?

Being in this study is completely voluntary. You do not need to participate in this study if you do not want to. If you do choose to participate, you can withdraw at any time.

(8) Alternatives to study participation

If you decide not to take part in this study, you can still continue to receive standard TB assessment, treatment and care at Daru General Hospital through the South Fly District TB program.

(9) Confidentiality

Your personal information will not be shared with anyone outside of the TB program, and any documents relating to you will be stored in locked cabinets and password protected computers. Data collected for the study will be have your name and any other information that can identify you, will be removed before being any results are published.

(10) What is the cost of taking part in the study?

There is no cost to participate in this study. All TB testing and treatment is provided free of charge.

(11) Will I get paid for taking part in the study?

No, you will not be paid for taking part in this research, but all TB testing and treatment is included free of charge.

(12) How do I find out the results of this study?

At the end of the study an information sharing workshop will be held. A plain language results information sheet will be handed out and the study team will provide one to you. The findings will be presented to the provincial health office and national department of health. It is expected that the study will be made available to the scientific community through publication in academic journals without any of your personal information, such as your name, being published.

(13) What if I need further information about the project or have a problem?

Once you have read this information sheet, a member of the team will talk to you further and answer any questions you may have. If you would like to know more, please feel free to contact one of our local researchers through the Burnet Institute office at Daru General Hospital: **Lucia Fernandez-Gonzales, Burnet Institute at Daru General Hospital or by email: lucia.gonzalez@burnet.edu.au or telephone: 79825115**

Any person with concerns or complaints about the conduct of the study can contact **Lucy Morris** at the Provincial Health Office (**Phone +67571508697**), Daru, Western Province or by email **lucymorrisdaru@gmail.com**

Appendix 5.3: Study standard operating procedures

ESCAPE-TB: Enhanced screening and preventive therapy for TB in Daru, South Fly District, Papua New Guinea

Version 8. April 2019

Manual of Standard Operating Procedures

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1. Terminology and abbreviations

TB	Tuberculosis
LTBI	Latent TB infection
IC/index case	Patient diagnosed with TB disease whose household contacts are investigated
HIV	Human Immunodeficiency Virus
DGH	Daru General Hospital
DEO	Data Entry Officer
TBDC	TB Diagnostic Centre (cough triage facility at DGH)
DSTB	Drug Sensitive TB
MDRTB	Multi-drug Resistant TB
HHISP	Health and HIV Implementation Services Provider
WV	World Vision
DART site	Daru Accelerated Response for TB treatment site
HMT	Household Mapping Tool
CHW	Community Health Worker
HEO	Health Extension Officer
MUAC	Middle upper arm circumference
PHO	Provincial Health Office
CXR	Chest Xray
CT	Contact tracing
EMRS	Electronic medical records system (Bahmni)
PEC	Patient Education and Counselling

2. Overview

The purpose of this manual of standard operating procedures is to provide guidance for program staff working on the *ESCAPE-TB: Enhanced screening and preventive therapy for TB in Daru, South Fly District, Papua New Guinea* operational research study. It provides step by step information on contact screening and testing procedures to determine suitable candidates for preventive therapy, identify symptomatic contacts with appropriate linkage to further TB evaluation, how to monitor study participants and data management information.

3. Human Resources

The study will utilise and train existing TB program staff on study procedures. The existing household contact tracing team will be involved in the initial screening, tuberculin skin testing (TST) including other test to exclude active TB and the treatment. Additional HR will be recruited depending on defined need in the course of the implementation. The follow up phase will involve TBMOs, the TBDC HEO and the study coordinator.

Roles and responsibilities

Western Province	PHO, Rural District Health and PHA as Provincial leadership
HHISP	HR supports for contact investigations and PT
DGH	Technical counterpart and link to care
World Vision	Support for PT site arrangement and Treatment supporters in follow up of CT and PT
Burnet Institute	Overall responsible for technical lead and managing the programmatic implementation of CT and PT including training the all staffs, mentoring and supervision of the activities
TB Case Manager	The case manager will initiate household mapping tools (HMT) for all bacteriologically confirmed cases (both DS and DR TB). The case manager also will get verbal consent and date to conduct household contacts screening and will distribute weekly during the case manager meeting
Contact tracing team (HHISP)	The contact tracing team allocated according to DART sites will visit the household with a treatment supporter working in the respective DART site. The contact tracing team is responsible for coordinating the time for the initial screening visit with the consent of the index case/head of household; screening for TB related symptoms, and data collection. The CT team will refer as necessary any screening positive TB related symptoms to the TB Diagnostic Centre (TBDC) where further investigations will be conducted. The CT team member (specifically trained in health education) will provide education regarding TB disease, TB infection, study participation. All contacts will be offered participation and asked to sign a consent form as per the study protocol. The CT team will conduct TST's for those DR-TB contacts who are negative for TB related symptoms following

	the ESCAPE TB protocol as below: • Educate the family on TB, its transmission, infection, symptoms, testing and treatment • Purpose of TST • Procedure of TST • Informed consent • Perform TST • Plan for follow up (reading and recording the TST results) • Conduct follow-up visit The CT team will revisit index case's house to read and record the TST results. Those TST positive and under 5 years will be referred to the DART site for HEO/clinician evaluation and initiation of treatment of latent TB infection after exclusion of active TB disease. The CT team will refer all asymptomatic under 5 to the DART site for HEO/clinician evaluation and initiate PT for DS TB accordingly. The CT team will also visit households for follow up screening of contacts who do not commence treatment for LTBI.
Screening team leader	The screening team leader is responsible for overseeing the activity of the household contact tracing team, ensuring timely screening occurs and accurate data collection, reporting and management in close collaboration with Burnet' technical team.
HEO	The HEO will be will be responsible for assessing eligibility for treatment for LTBI, and the prescription of treatment and follow up of the children under treatment according to protocol. The HEO will update HMTs weekly and will make the list of those has not attended at referral site (TBDC and PT site) and follow up through CT team. He/she will also record correct data in the treatment enrolment form during initiation and follow up of the PT treatment. The HEO also will support DGH TBDC in reviewing household contacts who screened positive for TB related symptoms and conduct further investigations and commence treatment as necessary.
Data entry officer	The data entry officer will record the paper based recorded data into Bahmni (EMRS) both for CT(HMT) and treatment of latent TB infection(Treatment Enrolment and Monitoring form)
Case finding coordinator (Burnet Institute)	The case finding coordinator is responsible for coordinating the overall implementation of the research in the field. They will be responsible for ensuring staffs are trained appropriately and that study procedures are followed. They will support the HEO to ensure appropriate assessment of eligibility for

	commencement of treatment for LTBI, prescription of medicines and ensure appropriate follow up occurs. They will be responsible for reporting of adverse events in line with relevant ethics committee requirements.

Index patients

Bacteriologically proven TB cases (both pulmonary & extra-pulmonary) will be identified as index patients for the study.

Bacteriologically-proven TB index patients will be defined as those whose sputum or other specimen is:

- MTB positive based on the PCR-based sputum test Xpert MTB/RIF; AND
- DS TB defined as Rifampicin (RIF) sensitive on Xpert; OR
  MDR TB defined as Rifampicin (RIF) resistant on Xpert, OR has phenotypic resistance to rifampicin and isoniazid on DST, OR has rifampicin and isoniazid resistance on other approved molecular assays.

The date of diagnosis of the index patient is defined as the date of reporting of the first positive test result showing GeneXpert positive and/or RIF resistance on Gene-Xpert, or (for MDR TB) a positive DST showing rifampicin and isoniazid resistance.

An index patient is defined as: "The initially identified case of new or recurrent tuberculosis in a person of any age in a specific household in which others may have been exposed to tuberculosis". If there is more than one member of the same household receiving treatment for TB at the time the contacts are enrolled, then the patient with TB who was diagnosed first is considered as the index patient. This does not necessarily infer the direction of transmission. Individuals from the same household who have previously completed treatment or who are currently on treatment (by the time that household contact screening and study enrolment occurs) would not be considered as index patients in this study.

Eligibility of household contacts

A **household contact** is defined as: Any person who lives (including spending time during the day) in the same house of index patient in the past 3 months

Inclusion and exclusion criteria for enrolment of household contacts in the study are as follows:

Inclusion criteria	Exclusion criteria
• Any age • Contacts of DS-TB or DR-TB index cases • Living in the same household as the index patient within the previous 3 months	• Contacts of pre-XDR and XDR-TB index cases • Unwilling or unable to provide informed consent • Unwilling to provide assent (for minors aged 10-17) • Suffering from a condition likely to lead to uncooperative behaviour (e.g. severe psychiatric illness or alcoholism) • Contacts who indicate they are planning to leave Daru within the treatment period (including follow-up)

4. Initial household screening visit

Materials required

- Household mapping tool
- Participant information sheets (in 4 languages)
- Consent forms (in 4 languages)
- Study enrolment forms
- MUAC tape
- Weight scales (standing)
- Linkage forms
- Tuberculin test equipment (see section 5 – *TST Placement and Reading*)
- TST card

Recruitment of participants and informed consent procedure

Recruitment of participants will occur during household contact screening visits. All bacteriologically confirmed TB index cases registered, who verbally consent to household contact investigations, will have their household contacts approached for participation.

All household contacts will be informed of the purpose of the study and what their involvement would require, and will be provided with information sheets and ample opportunity to ask questions. If they voluntarily agree to participate, a consent form needs to be signed by the participant (or parent/guardian if <18 years), the study staff member and a witness (if the participant cannot read and understand the consent form for themselves). Those choosing not to participate in the research may still undergo symptom screening and referral for TB investigations and treatment as standard-of-care through SFD TB program – any data collected from these individuals during routine screening will not be used for the study. See Annex 1 for patient information and informed consent documents.

Use of the Household Mapping Tool:

In line with current standard operating procedures for contact investigations, a Household Mapping Tool (annex 3) will be initiated when a new TB index patient is registered. The case manager will document information relating to the index patient at initial registration:

- Patient demographics
- TB treatment registration number
- TB type (pulmonary or extra pulmonary)
- Resistance pattern
- Smear result
- Gene-Xpert results
- HIV status
- Any other family member currently on TB treatment
- DART site the index patient is attending/will attend for treatment.

The case manager provides the contact tracing team with the HMT allocated for the index patient at a weekly case management meeting.

The member of contact tracing team, in consultation with the index patient, will schedule a date and time for contact screening to occur in the household when as many household contacts can be present as possible. The member of contact tracing team (usually the staff member allocated to health education and promotion) attends the household at the agreed time explaining the purpose of the screening and project. They are provided with education, supported through the reading of the patient information form. If the household members are willing to consent screening is undertaken. Following this all contacts who are screened as positive will be referred to TBDC for further evaluation. For those who are screened negative for TB related symptoms a TST will be placed. If there are household contacts not present during the initial visit, further screening visits (up to a maximum 3) may be required in order to capture all contacts.

A member of the CT team collects and records the following information for each contact on the HMT:

1. Household contact's name, age, gender, in the appropriate table (under 5 years; or aged 5 and over)
2. Relationship of the contact to the IC
3. Sleep location of the contact in relation to IC (same bed; same room; different room)
4. Symptom screening: Ask contact (or parent/guardian), if they have had the following symptoms, and document on HMT:
    - Cough, for 2 weeks or more
    - Fever, for 2 weeks or more
    - Night sweats, for 2 weeks or more
    - Recent weight loss (ask if clothes have become looser)
    - Any signs of extra pulmonary TB (lymph node enlargement, spinal deformity)
5. For contacts under <5 years (from 6 months to 60 months old) measure and document MUAC . For these children a measurement of <12.5cm will indicate positive symptom screening.
    - Moderate malnutrition: MUAC 12.5-11.5 cm
    - Severe malnutrition: MUAC <11.5 cm
6. Weight. For contacts <6 months old an assessment will be done of the child's weight using WHO's weight for age chart to exclude malnutrition.
    - Moderate malnutrition: -2 to -3(WHO Z score)
    - Severe malnutrition: Below -3 (WHO score)

If any TB symptoms or signs of extra pulmonary TB are present, or in children <5 years, or MUAC less than 12.5cm, the contact has *screened positive* and a **+** should be entered in the 'TB screening' column on the HMT.

If no signs or symptoms are present, the contact has *screened negative* and a **–** should be entered. In the case of a contact with acute symptoms (<2 weeks), the contact should be followed up in 10-14 days to determine if symptoms persist before a positive or negative TB screening is made. These patients should be noted 'Acute symptoms' in the Remarks column on the HMT and followed up appropriately.

The use of the HMT categorises contacts into the following categories:

Positive Symptom Screening

Any contact screening positive is referred to TBDC for further investigation as per Daru Household Contact Tracing SOP. A linkage form will be provided to the contact to attend the TBDC. The HEO/clinician evaluates all the contacts positive symptoms related to TB at TBDC. All contacts screening positive will be assessed for further TB investigations and assessment (Sputum, gastric aspirate, FNAB, chest x-ray etc.). The contact to be notified as soon the result will available. TB treatment will start as soon as

detected- bacteriologically or clinically. The other will link to CT team for TST after exclusion of active TB then will follow TST pathway.

Negative Symptom Screening

Any contact screening negative for TB related symptoms will be assessed with TST to determine presence of LTBI. Young children (<5 years) with acute symptoms (e.g. cough or fever <2 weeks) at the time of initial screening who do not meet the criteria for 'positive TB symptom screening' AND who are not so unwell as to require immediate referral for hospitalisation will need to be reviewed in TBDC 10-14 days post initial contact to review for suitability. If symptoms have resolved, they will undergo TST by the study team. If symptoms are persistent, they would be managed as a screening positive for TB related symptoms.

Once all household members have been screened, TST placed as applicable and referrals made as required, the HMT is returned to the screening team leader for initial data collation.

5. TST placement and reading

TST will be conducted either during the same household screening visit for all contacts or at a later visit (if required for a large household or numerous contacts absent from the home during the initial visit). The CT nurse will place and read the TST. TST will be undertaken on all household contacts on Monday, Tuesday, Wednesday and Friday – this will allow the reading of the TST result 48 hours after placement during weekdays.

Materials required

- Tuberculin Pure Protein Derivative (PPD) -contains multiple doses
- Cool box
- Frozen ice pack
- Thermometer (to remain inside cool box during transport in the community)
- 1ml syringe
- 26 or 27 gauge needle
- Cotton wool
- Kidney dish
- Alcohol skin swabs
- Sharps disposal container
- Disposable gloves
- Adhesive tape/micropore
- Pen or felt tip marker
- Tape measure/ruler
- TST card
- Foldable table or mats (at the discretion of the CTT Nurse)

- Foldable chair (at the discretion of the CTT Nurse)
- Plastic pillow with cover

Contraindications

Do not administer Tuberculin PPD to the following:

- Persons with known hypersensitivity to Tuberculin PPD or any components
- Persons who have experienced severe reaction to a previous tuberculin skin test for example (e.g., necrosis, blistering, anaphylactic shock or ulcerations)
- Persons with documented active TB disease and on treatment
- Persons with TB related symptom before exclude active TB
- Persons with extensive burns (alternate locations can be assessed and used if an option) or severe eczema (due to an increased risk of severe reactions)

TST is not contraindicated but does not need to be undertaken in those contacts who previously treated as bacteriologically proven cases.

The tuberculin skin test is considered both valid and safe to use throughout pregnancy (*CDC TB and pregnancy 2014*).
There is also no contraindication of TST for breastfeeding mothers.

Placing the test

Find a location away from others to reduce distraction and ensure sharps safety. The participant may sit and rest their arm on a table or pillow if available.

1. Check vial of Tuberculin PPD to ensure correct product, strength and expiry date. The solution is clear and colourless. Inspect the solution for any particles or discolouration– if these conditions are present the vial must not be used, reported and should be discarded.
2. The vial should be used for a maximum period of 30 days after the first injection is drawn, and then discarded. Write the date / time on the vial label when opened, and check at every use.
3. Introduce yourself to the contact. Ensure that the correct contact receives the test and the details on the enrolment form are correct. Check if the patient has any allergies.
4. Check if the contact has had the skin test before, if so, what was their reaction?
5. Identify appropriate location for injection. The preferred site is the volar aspect (palm side) of the left forearm. Choose a location free from any redness, swelling, irritated skin or palpable veins. If for any reason the left forearm cannot be used the alternate location (usually right forearm) should be very clearly documented.

6. Clean the area well with an alcohol swab and allow to dry (for at least 30 seconds) while preparing the injection.
7. Clean the rubber stopper on the vial with an alcohol swab and allow to dry (for at least 30 seconds). Attach the needle to the syringe and draw out 0.1ml of solution into the syringe. Remove the injection and after discarding the drawing up needle attach a new needle for the injections – this is to avoid using a potentially blunted need for the intradermal injection (if multiple injections will be undertaken in the same household only one drawing up needle need be used).
8. With the bevel facing up, insert the point of the needle into the superficial layers of the skin as an intradermal injection. Once approximately half of the needle length is inserted into the skin inject the solution slowly. Do not administer as intravenous, intramuscular or subcutaneous injection, as this will result in a test that is not interpretable.
9. If the injection is performed properly, a pale bleb will rise at the needle point, about 10 mm in diameter. Once the full dose is injected remove the needle.
10. Dispose of the needle and syringe immediately in a sharps disposal container.
11. If any blood is present at the injection site, it may be gently blotted with cotton wool/gauze but take care not to squeeze out the test fluid by compressing the bleb. Do not dress the site.
12. Educate the individual about possible skin changes and management of itch or swelling in the 2 days prior to test reading.
13. If injected improperly and no bleb rises, repeat the test immediately at a new site, at least 5cm away from original location. Mark near the new location with a small x to make it clear which site is to be interpreted.
14. Schedule with the contact for you to return to read the result in 48-72 hours. Record the date, time and location of the TST, and the date and time scheduled for interpretation on the TST card. This card is to be placed in the individual's clinic book. Update the HMT by recording all TST's placed.

Interpreting the test

1. Visit the household of the contact at the scheduled time. TST's cannot be accurately interpreted if >72 hours has passed since the skin test was placed.
2. Inspect the left forearm (unless an alternate location documented) carefully
3. Using a tape measure/ruler, measure in millimetres the diameter of induration (a palpable, raised, hardened area or swelling). Record this measurement on the HMT, even if it is 0mm. If there is a wider reddened area, do not measure this.
4. TST will be considered positive when:
    - The transverse diameter of induration is ≥10 mm regardless of BCG vaccination status,
    - Or ≥5 mm in a contact with HIV infection or severe malnutrition.

(Sanofi Pasteur Product Information for Tubersol, Tuberculin Purified Protein Derivative 2015)

The contact (or his/her parent/guardian) should be advised of the TST result. If TST is positive and contact is under 5 years of age, or HIV positive of any age, refer for review for eligibility for treatment for LTBI. As per exclusion criteria, contacts of pre-XDR or XDR-TB index cases will not be eligible for this study. However, a standard care of screening will be conducted and linkage to care.
If TST is negative and contact is under 5 years of age, a follow up TST will be conducted in 8-12 weeks and will be recorded in the follow up TST list.

If the TST result is positive and the individual is aged over 5 and presumed HIV negative counsel the individual (or their parent/guardian) regarding the result. Educate them about latent TB infection, signs and symptoms of active TB disease, and advise them to present early to DGH TBDC if they become unwell with symptoms. Educate about maintaining a strong immune system by eating well, getting enough rest and avoiding smoking, drugs and alcohol. Refer to speciality PEC services if further support and education is required.

Storage and transport of Tuberculin PPD solution

Tuberculin PPD solutions must be kept refrigerated between 2° and 8°C when not in use. Do not freeze. Vials taken to the household will be transported in a cooler box with an ice pack (frozen). Protect from light by storing in the dark at all times, except when withdrawing doses from the vial. Once opened the time and date of opening must be clearly documented to ensure that no vial is in use for more than 30 days. Vials must be discarded within 30 days of being opened.

Tuberculin Skin Testing:

Tuberculin PPD has been used extensively worldwide and is considered to be safe and generally well tolerated. With the administration of any agent or medication there can be a risk of adverse effects. It is possible that people receiving TST injections may experience some minor, temporary discomfort during the injection of Tuberculin PPD (often described to people to be similar to a “mosquito bite”), however it is not expected the injection will cause ongoing pain. It is possible that individuals receiving Tuberculin PPD may have allergic reaction, bruising at the site, or may develop a scar in the case of a strongly positive result. TST will be conducted by trained healthcare workers and the procedure is standard operating procedures. Any person experiencing adverse effects will be reviewed by the study team and taken to DGH as required. Any adverse event will be recorded; SAE reported to the overseeing ethics council (MRAC) and also to clinical expert group if required (see section 7) Adverse Event Monitoring and Reporting). With any procedure where the skin is broken, there is risk of infection. Prior to the injection, skin will be cleaned with an alcohol skin swab, to minimise the chance of skin flora being introduced at the injection site. Injecting equipment will be single use and will be disposed of immediately after use in a sharps disposal container; in

addition TST injections will occur in an allocated space away from others especially children to minimise risk of needle stick injury.

6. HIV testing

The CT team visiting the house will arrange HIV counselling and testing for child contacts of index cases who are known to be HIV positive. There is no need for HIV testing for other household contacts who are adults and otherwise present as healthy. Individuals requiring HIV testing will be referred to DGH for counselling and testing.

HIV positive contacts (of all ages) will access isoniazid preventive therapy as per national HIV/AIDS protocol. Positive result of HIV testing will be recorded onto the enrolment and monitoring form as B20.0. HIV test results to be tracked and entered into Bahmni separately. Study team personnel to transfer the result to the data entry officer for entry into that child's entry in Bahmni.

The clinical management of severe cases, i.e., those who are TST+, HIV+, MDR-contact, in the study will need to be discussed within the clinical expert committee or PI (via the collegium group).

7. BCG vaccination

BCG vaccine will be offered to children under 5 years who:

1. Have *not* been vaccinated with BCG previously
   AND
2. Have had 2 consecutive negative / non-reactive TST's (8-12 weeks apart) *OR*
3. Have completed a course of Preventative Therapy (in these children BCG must never be given during the course of treatment – it must be offered at the end of treatment).

8. Initiation of treatment for LTBI

Eligible participants identified during household screening will be referred to attend the PT clinic on a defined day (Tuesday to Thursday) for review by the HEO/clinician. Clinical assessment will be made to confirm the absence of active TB disease. Counsellors will educate and support the guardians on PT; if the participant satisfies all requirements and the parent/guardian has agreed commencement of therapy can then occur.

Materials required

- Study enrolment form and monitoring form
- Treatment card
- PEC team PT education tools

- Weight based dosing guide
- Preventive therapy register
- Medication
- Medicine cups and/or syringes
  Medicine supply bag

Medication prescribing

The HEO/clinician will thoroughly review the child contacts to exclude symptoms indicative of active TB disease, malnutrition/underweight and BCG vaccination. An assessment of the contacts risk of infection (for DS as TST not conducted) and review of the index case resistance profile (& their TB contacts) should also occur (resistance profile is indicated on the linkage form based on the IC registration number)

The HEO / clinician will prescribe treatment based on the resistance profile of the index case. Contacts of DS-TB will receive 3RH and contacts of MDR-TB (excluding pre-XDR or XDR-TB) will receive 6LFX. Dose will be based on the participant's weight. Drug choice and dose will be recorded on treatment card, Treatment Enrolment and Monitoring form, and preventive therapy register. The treatment card is used by the caregiver to support home treatment, and serves as a record of treatment to be retained in the participant's health book.

Contacts of DS-TB index cases – Rifampicin/Isoniazid (3RH)

Eligible contacts will be treated with RH daily for 3 months. See the table 1 for weight based dosing.

Table 1: weight based dosing of RH

Weight	***Dose***	***# Tablets***
4.0-7.9 kg	***75/50 mg***	***1 tablet***
8.0 – 11.9 kg	***150/100 mg mg***	***2 tablets***
12.0– 15.9 kg	***225/150 mg***	***3 tablets***
16.0 –24.9 kg	***300/200 mg***	***4 tablets***

In line with current SOP for isoniazid preventive therapy in Daru, participants receiving 3RH will also be prescribed 1-2mg/kg of pyridoxine daily for the duration of treatment for prevention of peripheral neuropathy.

Contacts of MDR-TB index cases – Levofloxacin (6Lfx)

Eligible contacts will be treated with levofloxacin daily for 6 months. The 2014 Sentinel Guidelines for MDR-TB in children recommends dosing in children aged <15 years is 15-20mg/kg once daily. See Table 2 for weight based dosing.

Table 2: Weight based dosing of Levofloxacin

Levofloxacin 250 mg Dose: 15-20 mg/kg		
Weight	**Doses**	**Number of tablet per doses**
< 2.9 kg	**Not recommended**	
3.0-3.9	**To be discussed with senior clinician**	
4.0-7.9	**125 mg**	**½ tab**
8.0-16.9	**250 mg**	**1tab**
17.0-24.9	**375 mg**	**1.5 tab**
25.0-29.9	**500 mg**	**2 tabs**

Medication preparation

The parent/guardian of children enrolled for preventive therapy will be instructed on how to prepare and administer the treatment, and will be assessed by the nurse/CHW for competence in preparing accurately. The first dose will be administered under supervision and if competent, the parent/guardian will be supplied with medications and any other equipment required.

If the parent/guardian is unable to prepare and administer the treatment accurately, supported home treatment options should be discussed and considered.

Patient Education and Counselling (PEC)

Basic education on TB infection and disease will be provided in the initial home visit by the Heath Educator as part of the explanation of the study. Further targeted education will be provided to any household members with further questions or concerns.

Following a positive TST result for a participant under 5, the participant and caregiver will receive an initial "Sleeping TB" education session prior to commencing preventive therapy. This session will focus on TB transmission and prevention, the difference

between TB infection and TB disease, and treatment for infection. This session will be held at the participant's home if possible, with inclusion of the family and key household decision makers to encourage support of the treatment process. If the session is not able to be held at the house it will be held at the treatment site prior to being seen by the clinical staff.

During their preventative therapy treatment period the child and caregiver will receive a further two standard counselling and education sessions to assess any issues and provide further education and encouragement. The second session will occur at one month of treatment and the last session will be held on completion of treatment with information provided on how to continue protecting the child and family from TB infection. The Standard sessions provided will follow the Sleeping TB Counselling guidelines and field summary and will utilise a flipchart and other educational tools.

Individualised counselling support will be provided at any other time during the treatment period at the request of the caregiver or program staff.

All counselling and education sessions conducted by counselling staff will be documented in the Sleeping TB hardcopy register and entered into the counselling section of the participant's record in Bahmni.

9. Follow up visits

Participants commenced on treatment for infection will attend follow up visits as per the below table. Follow up will be conducted by the preventive therapy clinical team, during the PT clinics. Follow up information will be recorded on the Patient Enrolment and Monitoring Form.

Time	Visit Purpose	Clinical activity	PEC follow up
D-	Assessment / preparation	• TB symptoms screening • Confirm eligibility for treatment	First education session
D0	Assessment Initiate PT	• Confirm resistance profile of index case • TB screening symptoms negative • Exclude malnutrition/ underweight • BCG vaccination status • Weight (WT) recorded • Train the caregiver on dose and give/prepare medicine	First education session (if not already delivered)
D14	Follow up	• TB symptoms screening • Side effects • WT • Record any missed doses • Review/refill medication • Next visit date	

M1	Follow up	• TB symptoms screening • Side effects • WT • Record any missed doses • Review/refill medication • Next visit date	
M2	Follow up	• TB symptoms screening • Side effects • WT • Record any missed doses • Review/refill medication • Next visit date	Second education session
M3 (if on 3RH)	Assessment and Assignment of outcome	• TB symptoms screening • Side effects • WT • Record any missed doses • Record outcome	
M3, M4, M5 (if on 6LFX)	Follow up	• TB symptoms screening • Side effects • WT • Record any missed doses • Review/refill medication • Next visit date	
M6 (if on 6LFX)	Assessment and Assignment of outcome	• TB symptoms screening • Side effects • WT • Record any missed doses • Record outcome	
Post treatment M9(3RH) and M12(6 Lfx)		• TB symptoms screening • Link to TBDC if screening positive for any TB related symptoms	

10. Treatment outcomes

All participants receiving treatment for LTBI will have an outcome assigned at the end of treatment (3 months for those on 3RH, 6 months for those on 6Lfx). The outcome will be documented on the caregiver treatment card, the Patient Enrolment and Monitoring form, and in the preventive therapy register. Outcomes will be defined as follows:

Completed

Participant completed the full prescribed course of treatment and remained asymptomatic of TB during the entire treatment period

Lost to follow up

Participant's treatment was interrupted for ≥1 consecutive months of 3RH and ≥2 consecutive months of 6Lfx regimen.

Died
Participant died for any reason during the course of treatment

Failed
Participant developed active TB disease at any point during the course of treatment if active TB was excluded at the time of initiation of PT

Transferred out
Participant transferred out to another health facility with a referral to continue therapy, but whose outcome is unknown

Treatment discontinued
Course of therapy discontinued for reasons other than developing TB disease, e.g.: severe side effects; withdrawal of consent. Reason for treatment discontinuation must be documented on Patient enrolment and monitoring form

11. Management of treatment interruption

For participants receiving 6 months of treatment for LTBI (6Lfx), treatment interruptions greater than or equal to 2 months will require a complete restart on a full course of treatment. For treatment interruption lasting less than 2 months, the participant should continue and finish the remainder of the course.

For participants receiving 3 months of treatment for LTBI (3RH), treatment interruptions greater than or equal to 1 month will require complete restart on a full course. For treatment interruption lasting less than 1 month, the participant should continue and finish the remainder of the course.

Any participant with adherence issues should be referred to the PEC team with their parent/guardian for support. Supportive home treatment options should also be considered for these patients.

12. Medication dispensation and accountability

Medications will be dispensed at commencement of treatment and at follow up visits, with supply given to last until next scheduled follow-up appointment plus ten days' buffer. Contacts will be required to return medicine packs at the next visit, and any remaining tablets will be counted by the healthcare worker to determine adherence. If doses are missed, the participant will be referred to the PEC team for counselling. The number of missed doses will be recorded monthly on the Patient Enrolment and Monitoring Form. Non-adherence will also be reported to the treating clinician. Treatment interruption will be managed as described in section 10 of this SOP.

13. Management of side effects and adverse event reporting

Upon commencement of treatment, contacts prescribed 3RH (and their parent/guardian) and 6 Lfx will be educated on common side effects and presenting symptoms, and will be advised that if any of these symptoms arise they should present immediately to the PT clinic or to Daru General Hospital, for further investigation.

Possible side effects associated with the use of Rifampicin/Isoniazid

(WHO companion handbook)

- Hypersensitivity reactions.
- Orange staining of body fluids
- Rash and pruritus
- Gastrointestinal upsets, flu-like syndrome (usually only with intermittent administration).
- Hepatotoxicity.
- Hematologic abnormalities (thrombocytopenia, haemolytic anaemia)
- Other reactions, including optic neuritis, arthralgia, CNS changes, drug induced lupus, diarrhoea, and cramping with liquid product.
- Peripheral neuropathy- Isoniazid should be accompanied by vitamin B_6/pyridoxine when available, to prevent peripheral neuropathy. As noted in section 7 above, contacts receiving 3RH will be prescribed 1-2mg/kg of pyridoxine daily for the duration of treatment.

Contacts receiving 3 RH for treatment of LTBI do not require baseline or routine monitoring of liver function, except in the following high risk groups:

- History of liver disease
- Chronic liver disease
- HIV infection

It is not expected the eligible contacts for treatment of LTBI will have any of the above co-morbidities. In the case of HIV contacts commencing on treatment for LTBI, baseline testing for serum aspartate aminotransferase, alanine aminotransferase, and bilirubin will be conducted, with monthly follow up testing conducted during treatment for those with baseline abnormalities.

Possible side effects associated with the use of Levofloxacin

- Nausea and bloating
- Headache, dizziness, insomnia and tremulousness.
- Rare tendon rupture, arthralgias (can usually be treated symptomatically)
- QTc prolongation, Hypoglycaemia

Participants/caregivers will be instructed to notify a health care provider immediately if any of the following occur:

1. Pain, swelling or tearing of a tendon (such as back of your ankle, elbow, etc) or muscle or joint pain
2. Rashes, hives, bruising or blistering, trouble breathing or tightness in chest
3. Diarrhoea
4. Yellow skin or eyes
5. Anxiety, confusion or dizziness

Participants receiving either 3RH or 6Lfx will be assessed for side effects and severe adverse events at each follow-up visit. Presence or absence of side effects will be recorded on the Patient Enrolment and Monitoring form at each follow-up visit, and any adverse events (gravity/severity) will be recorded on the back of the Treatment Enrolment and Monitoring Form.

Contacts experiencing adverse events will have further diagnostics and/or treatment as deemed appropriate by the clinician. As per South Fly District TB Program standard operating procedures, adverse events will be graded for severity using the Division of AIDS scale in Table 3.

Table 3: Grading of adverse events

Common Terminology Criteria for Adverse Events (CTCAE) scale

GRADE 1 MILD	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**	**GRADE 5 DEATH**
Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated.	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated.	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated.	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent disability or death.	

Treatment will be discontinued in the event of a grade 3 or grade 4 toxicity. Grade 3, 4 and 5 toxicities must be reported to the Principal Investigator immediately and to the clinical expert group.

The process for reporting adverse events is in line with PNG National Department of Health will be followed, and this will be instigated by the Case Finding leader/Principal Investigator.

14. Follow up of the contacts

The contact eligible enrolled or not enrolled in the study protocol for whatever reason will be followed up 6 monthly as follows:

1. The contact under 5 years of age, TB symptoms screening negative and TST positive/reactive (DR TB contacts) but refused PT treatment will be followed up for TB related symptoms after 6 month of initial screening
2. The contact under 5 years of age, TB symptoms screening negative and TST negative/non-reactive (DR contact), will repeat TST in 8-12 weeks. If subsequent TST is negative/non-reactive; BCG will be offered if not BCG vaccinated and followed up for TB related symptoms after 6 month of initial screening
3. The contact over 5 years of age, TB symptoms screening negative and TST positive/reactive(DR contact) will be followed up for TB related symptoms after 6 month of initial screening
4. The contact over 5 years of age, TB symptoms screening negative and TST negative/non-reactive(DR contact) will be followed up for TB related symptoms after 6 month of initial screening
5. The contact any age group, TB symptoms screening positive and diagnosed with TB will be followed up through standard TB care
6. The contact under 5 years of age initiated PT will be followed up at PT clinic according to define schedule and after 6 month completion of PT(outcome)

15. Data management

The screening team leader and the case finding coordinator will oversee the management of data and documents.

Study Enrolment Tracker

The Study Enrolment Tracker is an Excel workbook that can be used to track recruitment and key study activities on a weekly basis, as well as documenting participants who choose to withdraw or are removed from the study, and queries that study team members receive about the study.

Refer to the separate instruction sheet in the workbook for more information about recording information in this tracker.

Study ID Log

Unique study IDs will be assigned to study participants using the Study ID Log. The purpose of the log is to provide a unique link between participant names, study ID, index case, and any treatment registration numbers. This is to enable identifying participants (in case they need to be withdrawn from the study), and validating data for inclusion in the study dataset.

This log should be updated daily whenever participants are enrolled in the study and/or are assigned treatment registration numbers, and should be stored securely when not in use.

Refer to the instruction sheet at the front of the Study ID Log for further information about filling this log.

Consent Forms

Completed consent forms for participants enrolled in the study should be stored in an expanding file folder, in chronological order (by the date the consent forms were signed). The consent forms should be filed as soon as possible after the Study Enrolment Tracker is updated.

Separate sections in the file should be maintained for participants who are enrolled in the study, those who choose to withdraw from the study, and those who are removed from the study. Whenever a participant withdraws or is removed, their consent form should be refiled in the appropriate section and their withdrawal/removal documented in the Study Enrolment Tracker.

The file folder will be stored in locked cabinets when not in use.

HMTs

After the initial household screening, the HMTs are to be returned daily to the Data Entry Officer (DEO) for entry into the EMRS. Once entered, the DEO will return the HMT to the TBDC so it is available for further updates as presumptive cases present to the TBDC.

HMTs will be filed by index case registration number and be stored in the TBDC in locked cabinets when not in use.

The DEO will update the EMRS based on any new information recorded on the HMTs on a daily basis.

Patient Enrolment and Monitoring Forms

Patient Enrolment and Treatment Monitoring forms for participant active on treatment for infection will be maintained in an arch lever file (filed by participant registration number). These should be returned to the Data Entry Officer after each PT clinic for

updating in the EMRS. The file of active Patient Enrolment and Monitoring forms will be stored securely in the HHISP office at DGH when not in use.

Once the participant outcome is declared and all information is updated and checked in the EMRS, a separate file of closed Patient Enrolment and Treatment Monitoring forms will also be kept and stored in locked cabinets in the TBDC.

Follow-up Cards

Follow-up Cards will be opened for DR-TB contacts under age 5 with a positive TST (but active TB disease excluded) who agree to participate in the study but choose NOT to commence TB treatment.

These cards will be stored in an arch lever file (filed by participant study ID number). These should be returned to the Data Entry Officer after each follow-up visit for updating in the EMRS. The Data Entry Officer will document follow-up visits using the 'Followup Assessment' template in Bahmni.

The file of active Follow-up Cards will be stored securely in the HHISP office at DGH when not in use.

After all three follow-up visits are completed, a separate file of closed Follow-up Cards will also be kept and stored in locked cabinets in the TBDC.

Data quality assurance

Data quality assurance will be conducted by screening and PT team leader.

On a monthly basis, the screening and PT team leader will review a sample of Patient Enrolment and Treatment Monitoring forms, Follow-up Cards, and HMTs for completeness. These should be compared to data recorded in the EMRS.

Also on a monthly basis, the screening and PT team leader should review all available HMTs to ensure that data for all HMTs opened that month are up to date in Bahmni (all data is highlighted on the HMT after entry into Bahmni).

All Patient Enrolment and Treatment Monitoring forms and Follow-up Cards for participants who have **completed** treatment/all follow-up reviewed should be reviewed by the screening and PT team leader in full for completeness and accuracy of data recorded in the EMRS.

Any required corrections to data recorded in the EMRS should be reported to the Data Entry Officer for amendment. Corrections to data, or missing data, on paper forms should be reported to the relevant CT team members for follow-up and refresher training as required.

16. Documentation, tools and forms

Job aid checklist for CT nurse
Household Mapping Tool (HMT)
Participants Information Sheet (English, Tok Pisin, Kiwai versions)
Informed consent form (English, Tok Pisin, Kiwai & Gogodala versions)
Contact tracing Linkage form
TST card
Patient Enrolment and Monitoring form *(clinician facing)*
Treatment Card *(caregiver facing)*
Follow-up Card *(for DR TST+ contacts not taking treatment for latent infection)*

Preventive Therapy Register

All contact commenced on treatment for LTBI will be recorded in a preventive therapy register upon initiation. Each newly registered contact will be allocated a preventive therapy registration number. The following information will be documented in the register by the HEO:

Study participant's number
- Contact's name
- Age or date of birth, if known
- Sex
- Guardian name
- IC name and number
- TST date and result
- Date of BCG and scar if present
- Date commenced treatment

Type of regimen
- Dose prescribed – updated at each follow up visit
- Weight – updated at each follow up visit
- Outcome of therapy

Patient Enrolment and Monitoring form

A clinician-facing Patient Enrolment and Monitoring form will be allocated to participants commencing preventive therapy. The form will be initiated at treatment commencement and updated at each follow-up visit. The form will document dose, side effects, weight, presence of TB symptoms, and date of next follow-up visit at each follow-up visit. The card will also be used to document severe adverse events and counselling.

Treatment Card

A caregiver-facing Treatment Card will be allocated to participants commencing preventive therapy (Annex 5). The card will be initiated at treatment commencement and utilised as a prompt for the caregiver to ensure medication is administered daily. It will document dose in both milligrams and number of tablets required to give.

Preparation and administration instructions will be printed on the reverse side. It will be brought to follow-up visits during treatment to have weight and any dose changes recorded. The date of the next follow up will be recorded on the treatment card as a reminder to the caregiver. Outcomes will be documents at completion of treatment for the participant to keep as a record.

Follow-up evaluation will be recorded in the enrolment and monitoring form that include symptom screen, weight (clinical progress and dosage adjustment if required), and pill count to determine adherence and screen for adverse events. Monitoring for side effects will occur and documented as follows:

1. Adverse event name
2. Date started, date ended
3. Relationship to treatment for LTBI
4. Action taken with treatment for LTBI – medication stopped, or medication continued
5. Severity as per DAIDS grading
6. Outcome of adverse event

Follow-up Card

For under-5 contacts of DR index cases who test TST positive but who elect NOT to commence on treatment of latent infection, a Follow-up Card will be opened. The purpose of this card is to document follow-up visits at 6 months, 12 months, and 18 months after TST reading.

At each 6 month follow-up visit, monitoring for TB symptoms and/or development of active disease will be recorded.

Appendix 5.5: TB case detection cascade for household contacts by age group, 2017-2020: bacteriologically confirmed active TB

	0-4		5-14		15-34		35-54		≥55		Total	
Identified	1,051		1,229		1,133		885		607		5,537	
Screened (% identified)	954	(90.8%)	1,103	(89.7%)	1,032	(91.1%)	825	(93.2%)	493	(81.2%)	4,988	(90.1%)
Screened Positive (% screened) [1]	247	(25.9%)	228	(20.7%)	132	(12.8%)	164	(19.9%)	103	(20.9%)	962	(19.3%)
Active TB (% screened positive, bac+)	6	(2.4%)	9	(3.9%)	19	(14.4%)	14	(8.5%)	7	(6.8%)	67	(7.0%)
Co-prevalent TB* (% active TB)[2]	5	(83.3%)	3	(33.3%)	5	(26.3%)	5	(35.7%)	4	(57.1%)	27	(40.3%)
Incident TB# (% active TB)[3]	1	(16.7%)	6	(66.7%)	14	(73.7%)	9	(64.3%)	3	(42.9%)	40	(59.7%)
DS-TB (% active TB)	5	(83.3%)	4	(44.4%)	16	(84.2%)	11	(78.6%)	7	(100%)	48	(71.6%)
MDR/RR-TB (% active TB)	1	(16.7%)	5	(55.6%)	3	(15.8%)	3	(21.4%)	0	(0%)	19	(28.4%)
Treatment initiated	6	(100%)	9	(100%)	19	(100%)	14	(100%)	7	(100%)	67	(100%)
Completed Treatment	6	(100%)	9	(100%)	19	(100%)	14	(100%)	7	(100%)	67	(100%)
Contact screening yield (all forms)[4]	62	(6.5%)	19	(1.7%)	26	(2.5%)	23	(2.8%)	14	(2.8%)	159	(3.2%)
Screening yield (bac+)	6	(0.6%)	9	(0.8%)	19	(1.8%)	14	(1.7%)	7	(1.4%)	67	(1.3%)
Active TB (bac+)	6	(9.7%)	9	(47.4%)	19	(73.1%)	14	(60.9%)	7	(50.0%)	37	(42.1%)
Active TB (clinically diagnosed)	56	(90.3%)	10	(52.6%)	7	(26.9%)	9	(39.1%)	7	(50.0%)	92	(57.9%)

DS-TB: drug-susceptible tuberculosis; RR/MDR-TB: rifampicin-resistant/multidrug-resistant tuberculosis; bac+: bacteriologically confirmed

[1]Screened positive = symptom screening

[2]Active TB diagnosed within 90 days of household screening

[3]Active TB diagnosed between 91 and 360 days of household screening

[4]active TB / screened

Appendix 6.1: Publication - Majumdar et. al. (Frontieres in Tropical Diseases, 2023)

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Contact screening and management in a high-transmission MDR-TB setting in Papua New Guinea: Progress, challenges and future directions

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Daru, South Fly District, Papua New Guinea is a high transmission setting for multidrug-resistant tuberculosis (MDR-TB). An emergency response by the Government in 2014 established a high-quality model for treatment and care. Household contact screening and management commenced in 2016 with TB preventive treatment (TPT) for well young child (<5 years) contacts of people with drug-susceptible TB and later expanded to young child contacts of MDR-TB. The model of care is community-based and led by non-specialist health workers, under supervision. An electronic medical record system supports care, reporting and operational research. Community engagement and education has been central, with a concerted focus on peer-led counselling and patient-centred services to improve TPT uptake and completion. Challenges include the application of households as the unit of intervention for detection of active TB and TPT provision. Our implementation experience in Daru has highlighted significant population mixing dynamics with most transmission likely occurring outside the household. We propose a community-wide screening approach with the provision of TPT based on testing to include older children, adolescents, and young adults. As there is the possibility of MDR-TB infection irrespective of the drug susceptibility of the household index case, a novel option is a combination TPT regimen of 6 months of daily isoniazid and levofloxacin (6HLfx). A sensitive aged-related

algorithm to detect and exclude active TB is being developed. Ongoing community engagement, quality data systems with operational research to evaluate approaches are critical in high transmission MDR-TB settings.

KEYWORDS

tuberculosis, contact management, multidrug-resistant TB (MDR-TB), Papua New Guinea, contact screening, implementation research

Introduction

Tuberculosis (TB) is the leading infectious cause of morbidity and mortality in Papua New Guinea (PNG) (1, 2). The emergence and increasing transmission of multidrug-resistant TB (MDR-TB) is a major challenge (3). On Daru Island in the South Fly District of Western Province, PNG, there is an unprecedented MDR-TB outbreak with a TB notification rate of 2,021 per 100,000 for all TB and 594 per 100,000 for MDR/RR-TB (rifampicin-resistant) in 2015 (4, 5). In 2014, the PNG National Department of Health and Western Provincial Health Authority (WPHA) initiated an emergency response to MDR-TB, which has resulted in the stabilisation of TB notifications, improved treatment outcomes and a reduction in TB-related mortality (5, 6). A description of the geographical, social and demographic context in Daru, which is located in the transboundary region between PNG and the Australian Torres Strait, has been detailed elsewhere (7, 8).

A comprehensive community-based model of care for TB was established through the introduction of evidence-based practice, with significantly improved outcomes and introduction of novel tools including bedaquiline-containing treatment regimens (5, 9, 10). Community engagement and patient-centred support services have been central to delivery of care (11). An electronic patient-level medical record system (EMRS - Bahmni, Thoughtworks) was implemented in 2016 to support quality patient care, program monitoring and operational research (5, 9). The screening and management of household contacts of people with TB commenced in 2016. TB preventive treatment (TPT) for well young child (<5 years) contacts of drug-susceptible (DS) TB index cases was introduced in 2017 and extended to those of MDR-TB index cases in 2019 (12).

In Daru, as in many other high-transmission and resource-limited settings, best practice strategies and tools for TB and MDR-TB are often under-utilised or not prioritised (13). Active case finding through contact screening and TPT for eligible at-risk contacts is a programmatic priority. However, application to high transmission MDR-TB settings presents additional challenges that require specific considerations and novel approaches. Table 1 summarises the current approach, challenges and solutions for contact screening and management in Daru, PNG.

Current approach to household contact screening and management

In Daru, a dedicated public health TB Team consisting of a health extension officer (an auxiliary medical officer), nursing officers, community health workers and health promoters conduct contact screening for all newly detected bacteriologically confirmed pulmonary or extrapulmonary TB under the supervision of a medical officer. Following verbal consent by index cases or their guardian and the household head, contact screening occurs at the household level. Education is provided by trained health promoters to household contacts, who are defined as any person who lives in the same house as the index case within three months prior to diagnosis, including spending time during the day. Contacts with a positive symptom screen are referred to the TB diagnostic clinic for investigation and asymptomatic young child contacts to the TPT clinic. Young children are also screened for malnutrition which is managed according to local guidance and includes empiric treatment for soil transmitted helminths. Screening and management are provided by non-specialist nursing community health worker teams, in a community-based model of care (decentralised clinics) following standard operating procedures.

Detecting active TB in contacts

TB detection with treatment of disease is a critical role of contact screening and management along with determining eligibility for TPT. In Daru, there is a TB diagnostic clinic in the hospital where contacts with TB-related symptoms are referred for further investigation including chest radiography (CXR) and appropriate specimens such as sputum or lymph node aspirate for Xpert Ultra as per PNG and World Health Organisation guidelines (14). If RR-TB is detected, a specimen is

sent to the national laboratory for culture and drug-susceptibility testing and molecular assays for early diagnosis of fluoroquinolone-resistance. Gastric aspirate and/or stool samples for Xpert Ultra are taken from symptomatic child contacts unable to expectorate sputum. Asymptomatic contacts are not routinely referred for investigation, including asymptomatic young child contacts who are eligible for TPT.

TB preventive treatment

The provision of TPT to eligible household contacts is widely recommended but implementation in resource-constrained settings remains limited (1, 15). TPT should be routinely offered to well young child (<5 years) household contacts of people with confirmed or presumptive pulmonary DS-TB (16). The protective efficacy of TPT is well established (17) and the recently recommended shorter regimens are associated with high rates of completion and very few adverse events (16). The program in Daru was the first in PNG to systematically introduce a community-based model of TPT in 2016 using 6 months of daily isoniazid (6H) for young child contacts. A TPT regimen of 3 months of daily rifampicin and isoniazid (3RH) – recommended by WHO in 2018 – has been associated with high uptake, completion and safety in young child contacts under programmatic conditions in resource-limited settings (18). The availability in PNG of dispersible, child-friendly combined formulations for active TB since 2016 (19), led to the

TABLE 1 Contact screening and management – current approach, challenges and solutions in Daru, PNG 2017 - 2022.

Program Area	Approach to date	Challenges and considerations	Solutions and future directions
Model of contact screening and management	• Community-based (decentralised clinics) • Non-specialist public health team • Health promoters and education • Integrated screening for malnutrition and treatment for helminths in children <5 • Standard monthly follow up, including education and counselling if required	• Human resource shortage • Operational interruptions to CXR, laboratory and internet • COVID-19 impacts led to suspension of contact investigation • Large multigenerational households and contact networks (kinship, visitors) – definition of household	• Community-wide screening: detect, treat, prevent approach with evaluation • Task-shifting to nurses and community health workers • Technical partner implementation support • Households as unit of intervention
Detecting active TB	• Referral to hospital, dedicated TB diagnostic service • Gastric aspirate, lymph node aspirates and stool samples performed for mWRD e.g. Xpert Ultra • Chest radiography (CXR)	• Excluding active TB in children and adolescents • Optimal use of CXR – as abnormalities require follow-up	• Excluding active TB in children and adolescents with sputum for mWRD and CXR • Optimal use of CXR, consider in all >10 or >15 • Computer-aided detection of CXR >15
TB Preventive Treatment (TPT)	• TPT to child contacts <5 (and people living with HIV) • Shorter TPT regimens: 3RH • 6Lfx if evidence of infection (TST positive)	• Household exposure may not correlate with resistance of infecting strain as transmission occurring outside the household and multiple index cases • Who to test for TB infection • Optimal TPT for a high MDR-TB setting • Fluoroquinolone resistant exposure	• TPT for TST positive in 5-34 years • TPT for <5 years according to household exposure • Novel combination regimen with 6HLfx • Individualised approach to fluroquinolone resistant exposure
Community education & patient education and support	• Community education and health promotion campaign to explain "sleeping TB" (TB infection) prior to TPT service initiation • Peer counselling model. With family based care • Visual tools and aides (education games) • Child-friendly space in TPT clinic	• TPT for the well • Structural barriers – poverty, low health literacy, overcrowding, food insecurity, • Stigma and trust • Mobile population	• Community advisory group to co-design public health activities and education materials • Engagement of priority populations • Continue peer-led model • Person-centred care
Program monitoring and data systems	• Paper-based household mapping tools for contact investigation • Electronic medical record system for data entry, management, reporting and analysis •Cascade of care indicator set (individual or longitudinal)	• Comprehensive guidance on tools, definitions and processes for contact screening and management not available • Resources required to support EMRS • The need for re-identification across multiple health interactions for care (no ID system)	• Continue EMRS and cascade reporting • Unique identifiers: health book with ID and verbal ID. Biometrics not feasible. • Cascades of care for quality improvement

mWRD, molecular WHO-recommended rapid diagnostics; DS, drug-susceptible; MDR/R, multidrug-resistant/rifampicin-resistant; RH, rifampicin and isoniazid; Lfx-levofloxacin; TST, tuberculin skin test; CXR, chest radiography; CAD, computer-aided detection; TPTTB, preventive treatment; EMRS, electronic medical record system; ID'identification.

successful implementation of 3RH for young child contacts of DS-TB in Daru from 2019.

In Daru, up to 20% of incident TB is MDR/RR-TB (5). TPT as 3RH or 6H may not be protective for child contacts of MDR-TB and is not recommended in that context (16). Furthermore, known exposure to DS-TB does not necessarily determine that infection is limited to a drug-susceptible strain only (20, 21). The optimal TPT regimen following infection with MDR-TB is unknown. A regimen that includes daily levofloxacin for at least six months (6Lfx) is widely used. Observational evidence from a number of settings suggests that a fluoroquinolone-based TPT regimen in MDR-TB contacts with evidence of TB infection (TBI) can substantially reduce the risk of developing MDR-TB, and with no significant safety concerns (22–26). The findings from two randomised-controlled trials of 6Lfx for MDR-TB contacts are expected in 2023 (27, 28).

The use of TPT in MDR-TB contacts requires an assessment of potential benefit versus risk, and benefit is greatest in contacts with infection (17). In 2019, tuberculin skin test (TST) was introduced in Daru to determine eligibility for 6Lfx as TPT for young child contacts of index cases with bacteriologically confirmed MDR-TB (without fluoroquinolone resistance) as part of a pilot project. This age group was selected as being high risk for disease due to care-giving relationships and high likelihood that exposure occurred in the household of the index case. A similar model of implementation was used as for 3RH for young child contacts of DS-TB, with the addition of TST. An operational research protocol with ethical approval was obtained and following informed consent, young child contacts with a positive TST and no evidence of disease were offered 6Lfx. To date, an effective model of care has been established with high uptake and completion.

Community engagement and patient education

Community engagement and education is critical to support contact screening and management, and especially to support TPT uptake and adherence given that this requires giving medication daily for months to a child or adolescent who is well. In Daru, several approaches are utilised to deliver education to people on treatment, their families and the wider community. An international community-based organisation has been providing TB health promotion and social mobilisation activities since 2011, focussing on enhancing detection and treatment support for active TB (6). A peer counselling model was introduced in 2017 involving People who have been Affected by, Living with or having Survived TB, known as PALS, who are trained and mentored to provide education and counselling support (11). The counselling program initially focused on support for people on treatment for active TB and expanded in 2018 to include families of children on TPT.

Locally tailored education materials including visual tools were developed, tested with community, and guides created for standard counselling sessions scheduled at key points of treatment. A child-friendly space with activities was initiated at the TPT follow-up clinic. Counselling and education are provided in the family's preferred language where possible. Due to the limited health literacy and linguistic diversity (>3 languages) of the people South Fly District, visual tools and aides have been important. The term "sleeping TB" was used to explain the concepts of TBI. Community education and health promotion campaigns to increase understanding of "sleeping TB" and TPT were conducted including promotion from the town mayor and local leaders, public education sessions at churches, schools, sports events, community locations and local radio. The above measures have contributed to high rates of adherence and TPT completion.

Program monitoring and data systems

Monitoring and evaluation of contact screening and management programs are essential. However, comprehensive guidance does not exist regarding tools, data definitions or processes for programs to implement contextually adapted solutions. The WHO has defined minimum data and indicator definitions for TPT and the Zero TB Initiative has outlined a comprehensive set of indicators for the search-treat-prevent approach (29, 30). The EMRS in Daru was adapted to include modules for contact screening and TPT in 2018. A household mapping tool that documents investigation of all close contacts of an index case is used as previously described (12). The public health team records patient data using paper-based records. A data entry team subsequently enters this data into the EMRS. Contact screening and management is monitored using a cascade-of-care framework for TB detection and prevention. The EMRS enables reporting of an individual-level cascade, rather than aggregate. Resources required to support the EMRS, including information technology expertise, programming skills and data entry capacity, are provided through partner support. Despite challenges, implementation has been successful, with the data system monitoring TPT uptake and outcome.

Implementation challenges and considerations

Operational challenges include a chronic shortage of health care workers, interruption of CXR services, laboratory reagents and power and internet outages. The availability of international partner support has been critical to the TB program in Daru since 2011. Adopting a community-based model with mobile

teams and task-shifting from medical and para-medical staff to nurses and community-health workers with training and technical support from partners has helped to address human resource issues. The COVID-19 pandemic has had a major impact on the delivery of TB services. From March 2020 until April 2022, contact screening was suspended initially due to public health restrictions and infection risks and subsequently health workforce shortages. Programmatic focus over this period was active TB treatment and care with case-finding limited to facility-based only (passive). Household contact screening and management restarted in April 2022.

Daru, and South Fly District have significant particular challenges in the social determinants of health which contribute to increased risk of TB transmission, with one of the highest measures of household poverty in the region, low levels of health literacy overcrowding food insecurity and low access to health services due to service availability, remoteness and lack of trust (7) (8). The TB program has had a concerted focus on community engagement, health promotion and patient-centred services. A major challenge has been identifying and reaching households which has been successfully addressed through the engagement of community leaders, household heads and community education. This patient and family-centred approach has built trust. Timely referrals for eligible TPT candidates for pre-initiation counselling also reduced delays in time to initiation of TPT. In the early implementation of TPT for young children, adherence issues were noted prompting an exploration and development of solutions for contributing issues through counsellors.

A Community Advisory Group, self-named TB Nanito Kopia Kodu (the Voice to Kill TB Forever) was formed from community consultations in late 2019 with members representing key stakeholder groups (e.g. churches, schools, businesses, key populations). The group's primary focus is providing community input and co-design for TB public health activities, including the development of community education materials and models to reach key populations such as adolescents and students, working adults (not present at home), prisoners, people with disabilities and the elderly. Accordingly, a comprehensive community education campaign has been developed with a participatory approach involving training of representatives from key populations.

Re-identification of individuals during multiple episodes across the screening and prevention cascades of care has been a particular challenge due to poor civil registration coverage (31). In PNG, people may give different names, age and residence from visit to visit with addresses not specific enough. Paper-based recording at multiple points of care also contributes to the problem by making it difficult to check a patient's details against existing information. The linkage of contacts to multiple index cases needs to be reconciled for reporting. This is currently addressed through local health worker and community knowledge of households and engagement *via* peer counsellors. Biometric systems have been proposed as a solution for patient identification, but cost, complexity and acceptability are barriers to implementing them. An immediate solution is patient-held records, such as health books or a card that can be issued and used to identify patients. However, these may get lost or not brought to patient visits. We have designed a potential solution for re-identification at low cost that supplements patient-held records with a memorisable unique identifier consisting of three common objects, represented with images. Even partial recall of this identifier can aid re-identification.

The primary challenge in Daru is the application of the household as the unit of intervention for contact screening and to deliver post-exposure management including detection of active TB and TPT. This is both from an implementation perspective and the fact that households may not be the optimal unit of intervention for timely detection of active TB and identifying those at risk of recent exposure for TPT (32, 33). The socio-cultural context in Daru, as elsewhere in PNG, involves large multi-generational family structures based on kinship. However, there are some unique features with significant overcrowding in settlements and frequent travel between mainland villages and Daru Island, often for extended periods of time. This results in large "households" with complex family structures and population movement. Therefore, the operational household contact definition used is broad and includes those who have spent more than one night in the household.

Our experience in Daru is that most transmission is likely occurring outside the household, as noted even in children in other high-incidence settings (32). The likelihood of exposure and infection occurring outside of the household increases with age. Adolescence is a peak age for close and casual social contact and so in a highly endemic setting such as Daru, the majority of the population may be infected by adulthood (34). TST testing in MDR-TB household contacts in Daru has demonstrated a high prevalence of infection similar to reported elsewhere (35). The majority of TB and MDR-TBnotifications are in older adolescents and young adults, with around 70% of TB notified in those 15-34 years (5). Furthermore, with large household sizes and a very mobile population, an individual can be exposed to multiple index cases concurrently, including DS and MDR-TB. Therefore, consideration of alternative approaches in Daru to household contact management are warranted.

Future directions – moving beyond household contact screening and management

Until recently in high TB transmission settings, recommendations for TPT have been limited to specific high-

risk groups for disease such as young child contacts and people living with HIV (16). Whilst important in reducing tuberculosis-related morbidity and mortality in these groups, the impact of TPT on community transmission by preventing new cases is small, likely negligible for young child contacts (32, 36). Therefore, a community-wide strategy has been considered in the design of an enhanced public health intervention and model of care that aims to increase TB detection and treatment while providing TPT to a broader population to reduce transmission in addition to TB morbidity and mortality (37, 38). Figure 1 outlines our considerations for a comprehensive detect-treat-prevent strategy in a high TB transmission setting by age.

First, programmatic scaling-up of contact screening and management that includes older children, adolescents and young adults in the community is planned. The 2020 WHO recommendations include a wider age range of TPT options for HIV-uninfected contacts (16). We therefore propose community-wide TST testing for Daru residents aged 5-34 years irrespective of household contact, with TPT provided to those with infection and no evidence of active TB, as part of a comprehensive approach to complement active case-finding. The model of community engagement and implementation described above will be applied and the household will be the unit of intervention. The application of a community-wide systematic screening for case detection aligns with recent WHO recommendations for settings with a TB prevalence of 0.5% such as Daru, and is based on new evidence of public health benefit (39). The decision to provide TPT for 5-34 years with infection is based on the following considerations: high-risk age group for active TB; high risk age group for transmission in the community; and lower risk of isoniazid-related toxicity due to TPT compared 35 years and older.

Second, in high transmission MDR-TB settings, consideration of a TPT regimen for older children, adolescents and adults that considers the possibility of infection with an MDR-TB strain irrespective of the index case is needed. A novel option is a combination TPT regimen of 6 months of daily isoniazid and levofloxacin (6HLfx) for 5–34 year-olds with evidence of infection and no active TB. This TPT regimen is chosen to effectively treat infection with either DS or MDR-TB as a positive TST cannot determine drug susceptibility. Whilst exposure to both is common, the majority (>80%) of TB in Daru is DS-TB. Isoniazid or rifampicin may not effectively treat infection with an MDR-TB strain. While it is plausible that levofloxacin alone may cover treatment of DS in addition to MDR infection, there is no definitive evidence of efficacy at present. There is circumstantial evidence that isoniazid may also be effective in the treatment of MDR infection (20). Rifapentine is currently not available in PNG and a three-drug regimen may have additional adverse effects over two. Therefore, isoniazid is included in the proposed regimen. Young child (<5 years) contacts can be managed as per the strain of the index case. The optimal approach for management of fluoroquinolone-resistant TB infection is uncertain and should be individualised.

Third, it is critical to exclude active disease especially in adolescents and adults. An optimal age-related contact management algorithm is required to mitigate the risk – individual and public health – of generating resistance including to fluoroquinolones. This risk needs to be negligible, similar to isoniazid and rifampicin (40, 41). In addition to symptom screening, the inclusion of CXR and sputum Xpert Ultra in the algorithm will provide high sensitivity for detection. The optimal age-related use of chest-radiography in asymptomatic, HIV-uninfected people aged 5–34 years to rule out active TB before TPT is unclear. WHO guidelines recommend that asymptomatic young child contacts or PLHIV do not require CXR before TPT initiation. It is likely that the same approach could be applied to all well children (<10 years) with infection without risk of not detecting sub-clinical disease. This is the approach that is being considered in Daru. In addition to a negative symptom screen, CXR will be routinely included in screening adolescents and adults (≥10 years), as it is

	< 5 years	5-14 years	15-34 years	35-54 years	55 years +
Potential impact on transmission	Minimal +/-	+	+++	++	+
Symptom screen	For all ages				
CXR if symptom screen negative	Not recommended	**Uncertain**	Recommended		
Test (sputum) for active TB and resistance with mWRD	For symptomatic and abnormal CXR		For all – symptomatic, CXR abnormal and consider in asymptomatic if able to provide sputum		
Test for infection for TPT initiation	Not required	Recommended			
TPT indicated	If TB-exposed and asymptomatic	If evidence of TB infection		Uncertain	
TPT regimen	**3RH if DS-TB exposure 6Lfx if MDR/RR-TB exposure**	**Consider combination regimen in high MDR setting: 6HLfx**			
TPT safety	+++	+++	++	+	+

FIGURE 1
Considerations for a comprehensive detect-treat-prevent strategy in a high MDR-TB transmission setting by age. mWRD, molecular WHO-recommended rapid diagnostics; DS-TB, drug-susceptible tuberculosis; MDR/RR, multidrug-resistant/rifampicin-resistant tuberculosis; RH, rifampicin and isoniazid; Lfx, levofloxacin; CXR, chest. NB. Different considerations apply in high HIV transmission settings and special populations.

important to exclude active TB with a sensitive algorithm prior to TPT initiation. Computer-aided detection of CXR is recommended for TB screening in people ≥15 and this will also be used for screening young adolescents (10-14 years). This is because adolescents with TB commonly present with adult-type disease such as with cavitation, most critical to rule-out before initiating TPT.

The significant health individual and health system burden of ongoing MDR-TB transmission is a compelling argument for the potential benefit of the community-wide approach to detect, treat and prevent DS and MDR-TB and likely outweighs potential individual treatment risks with 6HLfx (13, 42). Operational mixed-methods research will evaluate the impact, acceptability, feasibility and cost-effectiveness. The intervention will build on the local leadership, programmatic experience and platform of innovation that has been established in Daru. Ongoing engagement and placing the affected community at the centre of the response remains critical to success and towards ending tuberculosis in high-transmission settings.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

SM, SG and GKH contributed to conception and design of the study. GD, SB, TK, GC, SF, AM, JG, CM, TM, SU, SG and SM developed sections of the manuscript. SM wrote the first draft of the manuscript. All authors contributed to manuscript revision and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix 7.1: Optima TB modelling for SWEEP-TB: Summary

Policy Brief: Optimising TB Responses in Daru

Daru Island in Western Province, Papua New Guinea is the site of a public health emergency due to an epidemic of TB. The epidemic is characterized by high rates of both drug-resistant and drug-susceptible TB among the island's population of approximately 17,000 people. An emergency response to TB has been implemented in Daru, beginning in 2014. The response has been enabled by GoPNG, DFAT and World Bank investment and important progress has been made in improving case finding and treatment of active TB. However, the response to date has not yet had an appreciable impact on ending the epidemic. The public health imperative of reducing the social and health burden of the TB epidemic will require continued investment and, likely, expansion of the range and scale of interventions used in the response. The key questions to be answered in order to plan and implement a response that will end the epidemic are:

1. **What are the components (services and interventions) of an effective response in reducing the burden of TB in Daru?**
2. **How much investment is needed to reduce the burden of TB in Daru?**
3. **What is the most efficient way to invest money to respond to TB in Daru?**

The Optima TB model has been used to conduct a scenario analysis with the express aim of answering these questions to guide investment in and implementation of the response to TB in Daru. This analysis was commission by the National Department of Health, Western Province Health Office, World Health Organisation and supported by the Australian High Commission, PNG (DFAT) through the Burnet Institute's RID-TB project. Ethical clearance was not required as available routine programme data was used.

Methods

Optima TB is a population-based compartmental model that uses a linked system of ordinary differential equations to track the transmission of TB within and between context-specific population groups. The overall population is partitioned in two ways: by population group and by TB health state. TB infections occur through the interactions among different populations.

The model was applied to the TB epidemic in Daru. The population compartments for Daru included HIV-infected groups for populations aged 0-4, 5-14 and 15+ and non-HIV infected groups for populations aged 0-4, 5-15 and 15+. The compartments for TB health state allowed for latent infection; BCG vaccination; DS, MDR and XDR strains of active disease; as well as treatment and treatment outcomes. The model for Daru was calibrated using demographic data from the 2000 and 2011 PNG census and epidemiological data using **routine TB program reports from Daru BMU** 2011 -2017 on case detection, enrolment and treatment outcomes. These were used to adjust the parameters in the model so that historical rates of infection and treatment outcomes in the model were consistent with the known data.

The calibrated model was then used to explore future projections of **prevalence, incidence and deaths**. Scenarios were defined in terms of the effectiveness and coverage of different interventions in diagnosing, preventing and treating TB. The model was used to generate projections of the impact of each scenario on prevalence, incidence and death. The cost of each intervention was estimated using known expenditure and cost data from the TB program and was then included in the model to estimate the cost of implementing each scenario.

Results

The results of the epidemiological modelling showed that under current conditions:

- a rapid reduction in incidence per capita among children aged 0 to 4 years was occurring due to improved treatment and reduced exposure since 2014.
- Incidence per capita in other populations is projected to remain stable and is largely driven by activation of latent TB and reinfection.
- The total number of new active infections is projected to continue increasing in line with population growth, leading to higher future treatment costs

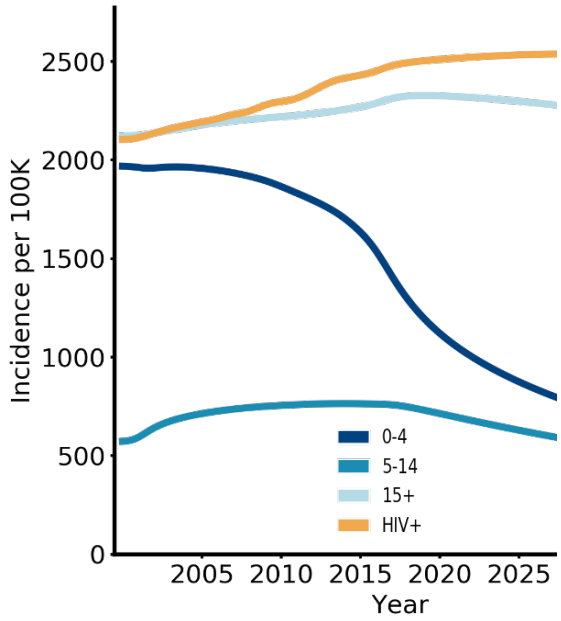


Figure 1: Projected incidence of active TB cases

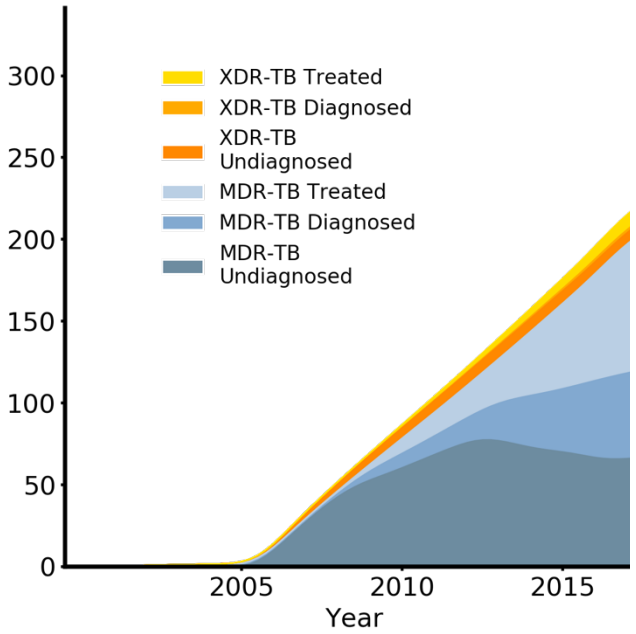


Figure 2: Projected number of people with drug-resistant TB

In summary, current levels of diagnosis and treatment are projected to lead to **stable prevalence rates** in the population, which results in an increase in absolute numbers due to population growth. Moreover, drug-resistant TB will represent **an increasing proportion of all TB cases**. Consequently, under current program conditions program costs will increase due to the growth in the total number of cases and due to the increase in DR-TB for which treatment is more expensive and complex.

Scenario analysis

The impact of the following five scenarios were explored using the model. The scenarios are presented in order with each scenario including all components of the preceding scenario while adding additional interventions:

A. Passive case finding and treatment of active disease
B. Scenario A + Active case finding through household contact tracing
C. Scenario B + Active case finding through population screening (SSI)
D. Scenario C + Preventive therapy for DS and DR TB through household contact tracing
E. Scenario D + Preventive therapy for DS and DR-TB through population testing and treatment for TB infection

Parameters were set for the scenarios as follows:

	Active TB			TB Infection		
Scenario	% probability of testing within 12 months	% cases found that are started on treatment	Treatment success	Diagnosis	Treatment initiation	Treatment success
A	60%	98%	80-85%			
B	85%	98%	80-85%			
C	95%	98%	80-85%			
D	95%	98%	80-85%	8 cases per active case	85% in children U5 70% in adults	70% in children U5 60% in adults
E	95%	98%	80-85%	90% probability of testing within 12 months from infection	90%	90%

Treatment modalities and the proportion of outcomes for diagnosed cases were kept constant at **current programmatic levels (ie real-world)** under each scenario. Sensitivity of testing through clinical diagnosis and GeneXpert for population screening for active TB was set at 95% in adults and 85% in children. The BCG vaccination rate in children aged 0-4 was modelled in the following scenarios: A 60%, B 75%, C 80%, D & E 90%.

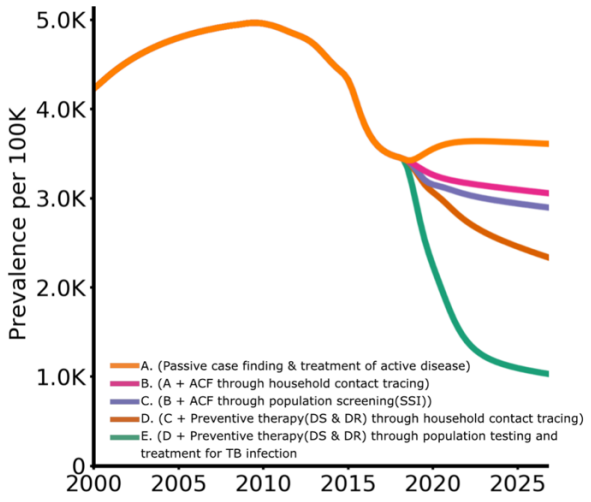


Figure 3: Estimated prevalence under modelled scenarios

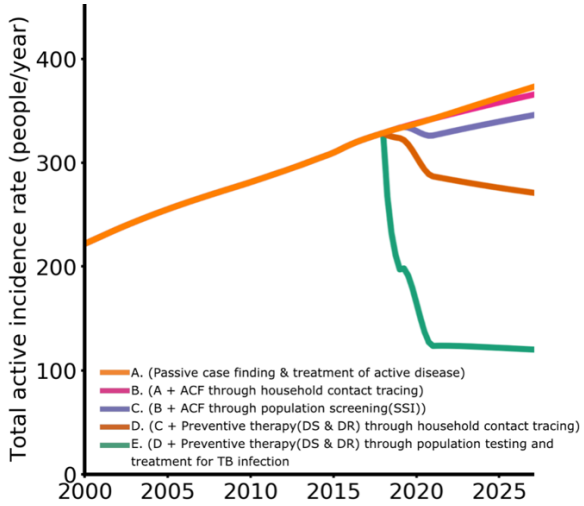


Figure 4: Estimated incidence of active TB under modelled scenarios

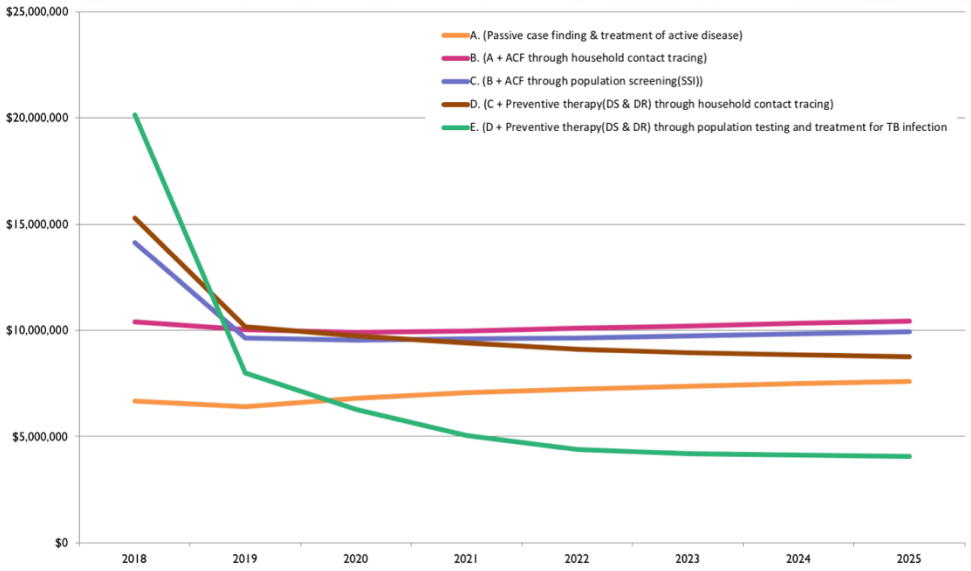


Figure 5: Projected annual implementation costs by year (PGK, not adjusted for inflation)

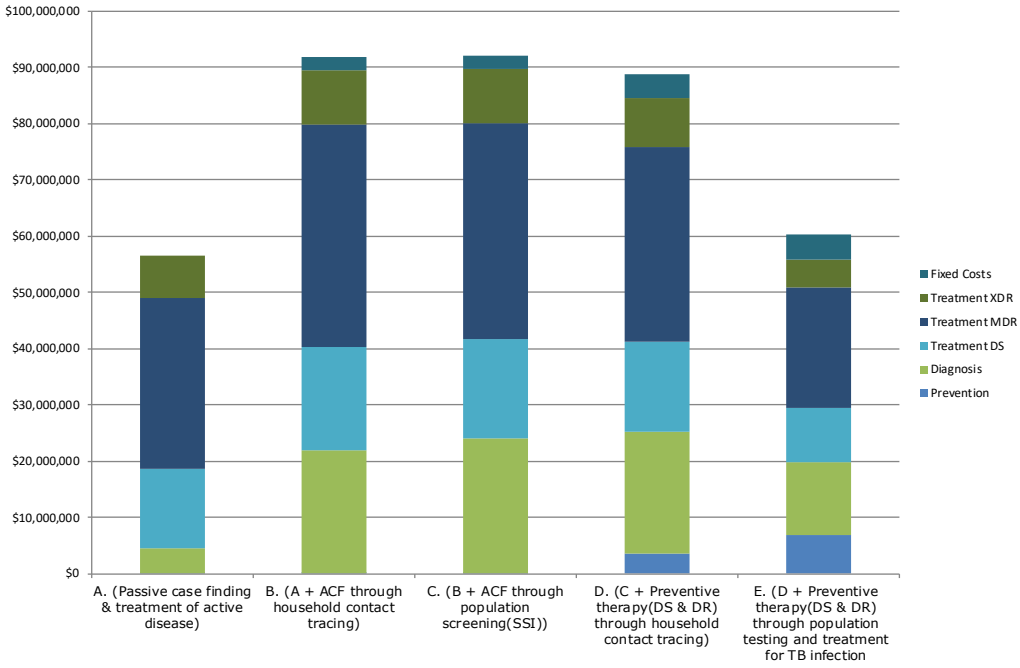


Figure 6: Estimated total implementation costs from 2015-2025 (AUD)

Conclusions and recommendations

Adopt a comprehensive search, treat and prevent approach (scenario E) to maximise impact on the epidemic and cost-effectiveness

- Scenario E is estimated to result in an 80% decline in the TB epidemic, to reduce mortality and to lower ratees of drug-resistant TB.
- Scenario E will be the least costly in the long term. It has the highest up front cost but results in a rapid reduction in incidence and prevalence and therefore reduces treatment costs for active TB in subsequent years due to the sharp reduction in cases needing treatment
- The external benefits of reduced TB prevalence have not been modelled and therefore the model likely underestimates all of the gains under scenario E
- The rapid reduction in TB can be more readily managed by the existing health systems with reduced risk of spread to other locations
- In comparison, active case finding without latent treatment will result in a much smaller reduction in prevalence and will result in continued increases in costs due to population growth.

Secure long-term financial investment in the response as a requirement for sustaining impact on the TB epidemic

- Ensure that the existing quality of case finding and treatment are maintained. Exploratory analysis using the model suggests that reductions in treatment quality and active case finding would negatively offset any gains made through population testing and treatment of TB infection

Optimize the model of care and utilisation and service effectiveness throughout the patient journey

The results of the modelling indicate that even with long-term population screening and treatment of latent infection there may be a persistent but lower level of TB transmission and active disease. Optimizing program efficiency throughout the patient journey, ie every step of the care cascade (search-treat-prevent) will increase the effectiveness of the interventions. The additional role of social determinants such as crowding and behaviours relating to care utilization should be explored as means of increasing the reach and coverage of TB services and reducing delays in seeking diagnosis and treatment for TB. As new innovations emerge, such as TB vaccines, their impact can be modelled.

Funding for this work was provided by the Australian Government through the RID-TB Project implemented by the Burnet Institute.

NATIONAL DEPARTMENT OF HEALTH

PNGAus Partnership

Burnet Institute
Medical Research. Practical Action.

optima DECISION SCIENCE

Appendix 7.2: SWEEP-TB Community Advisory Group: Terms of Reference

TERMS OF REFERENCE

TB Nanito Kopia Kodu Group

(the voice to kill TB forever)

Daru TB Elimination Community Advisory Group

Terms of Reference

Agreed March 2021

Background

Daru, South Fly District, has one of the highest rates of MDR-TB in the world. The Western Provincial Health Authority (WPHA – Daru General Hospital, South Fly District Health) and partner organisations (Burnet Institute, World Vision) have worked together to build a strong TB program that finds and treats TB *disease*. It has resulted in high treatment completion rates, good quality of care for patients using peer education and counselling, and screening of families of people on treatment for TB.

However, the spread of TB continues in Daru, and high numbers of people are still being diagnosed with TB each year. To eliminate TB in Daru, the next step is finding and treating TB *infection* (sleeping TB) in the community before it grows into TB disease. WPHA plans to screen, test and treat all residents of Daru for TB disease and infection (sleeping TB).

It is important that the planning and roll out of the island wide screening is led by the voice of the community. A group has been created involving representatives from different parts of the community who will give advice and guidance on the island wide screening and other TB elimination activities in Daru.

Purpose

The group will provide guidance on the design, planning and completion of TB elimination activities in Daru. The group represents the voice of the community of Daru.

Membership

The group is made up of representatives of key groups in the community, including representatives from:

- Community leaders
- Churches
- Schools
- Patient representatives
- Business houses
- Sports
- Special groups

The group aims to have equal male and female participation and representation from across the wards and corners of Daru.

The group is supported by staff of the TB Program, in particular Health Educators.

Meetings

The group will meet every 6-8 weeks on a day and time chosen by the group.

Only members of the group will attend the meetings, other people will not be sent on behalf of members if they are unable to attend.

Activities

1. Review and provide guidance into the design and roll out of TB elimination activities in Daru.
2. Check that activities meet the needs of the community.
3. Provide advice about how best to engage the community in TB elimination activities.
4. Review and provide feedback on community education materials.

Ways of working

The members of the group will represent the best interests of the community of Daru.

Interaction in the group will be respectful of differing views.

Participation in the group is on a voluntary basis.

Appendix 7.3: SWEEP-TB Community engagement materials

HIMARA IMEHE GO TB KO'OMIRITI DARU RUDO

YUMI BUNG WANTAIM NA RAUSIM TB LONG DARU

OUT OF DARU!

COMMUNITY EDUCATION HANDBOOK

Dear _____

Thank you for your commitment to educating
the people of Daru about TB.

This book is a guide to help you give awareness on TB.

It includes:

- Steps for planning your awareness session
- Tips for giving awareness
- A script to follow for awareness
- Information on common questions about TB
- A space to record information about your sessions

The TB team member who is supporting you is

_____

Their contact number is

_____

Contact them if you have any questions or would like any help.

STEPS FOR PLANNING YOUR AWARENESS SESSION

Follow these steps to help your preparation go smoothly...

1. Discuss with your group an ideal day and time for the awareness.
2. Arrange a suitable location that is big enough for the group size.
3. Inform your TB team support person of your confirmed time and venue.
4. Remind group members when it gets close to the date.
5. Prepare the venue space and any equipment needed (eg. speaker)
6. Practice your awareness presentation.

TIPS FOR GIVING AWARENESS

Take some deep breaths before you start to help settle you.

Enjoy yourself! If you are relaxed and happy your participants are more likely to engage.

Speak loudly and clearly - use a sound system if available.

Keep your participants interested with questions and discussions.

Give participants the chance to ask questions -
verbally or in writing if they don't feel comfortable speaking up.

TB INFORMATION

This information can be given during the awareness or can be used if participants ask for it.

2 Billion people, or one quarter of the world's population, are currently infected with TB infection (Sleeping TB).

In Daru, around **90%** of people who are diagnosed with TB complete their treatment- this is one of the highest completion rates in the world. This shows strong commitment from people on treatment and good support from the community and TB program.

In 2021 Around the world more than **10 Million** people were diagnosed with TB disease.

In PNG **28,200** people were diagnosed with TB disease.

In Daru, **443** people completed treatment. Another **424** people were diagnosed with TB.

SUGGESTED AGENDA FOR AWARENESS SESSION

Activity	Description	Lead
Survey of TB understanding	Survey with a small group to check their understanding of TB before the awareness Done while participants are arriving	TB staff member
Welcome and introductions	• Welcome to the session • Introductions of the group • Explanation of the session	You
TB education	Education on important TB information using: • Flipchart • Script in this guidebook • Giant lungs	You
Questions and discussion	• Questions invited in writing or verbally • Discussion of answers	You and TB staff member
Closure	• Thanks to the participant • Closure of the session s	You
Repeated survey of TB understanding	Survey repeated with same small group to check their understanding of TB after the awareness Done while other participants are leaving	TB staff member

SCRIPT FOR AWARENESS

This script is designed to be used with the SWEEP-TB community education flipchart. The words in orange are a guide for you and don't need to be said. The blue words are questions that you can ask the group.

Introduction

We're here today to talk about an issue that is affecting every household in Daru- TB. To begin with I will go through some information about TB. After this we will have the chance to discuss any questions you have. If there is anything that I say that is unclear please let me know and I will explain it more with the help of the TB team support person.

1

Turn to Flipchart page 1

WHAT IS TB?

Tuberculosis, or TB, is a disease caused by a germ. It has been around since ancient times and still affects millions of people around the world each year.

The good news is that TB is curable with medicines.

2

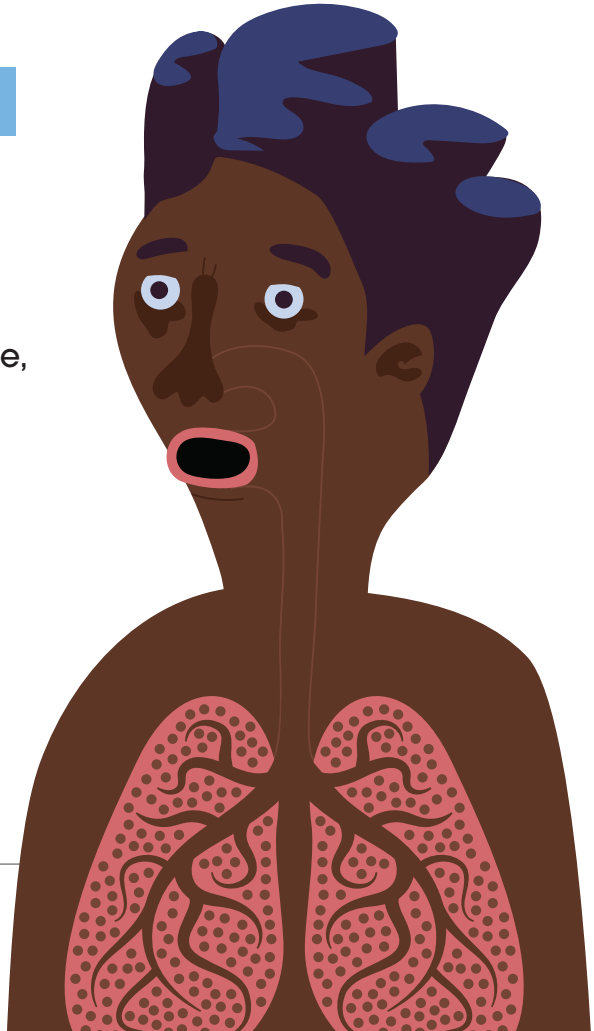
Turn to Flipchart page 2

TB SPREADS THROUGH THE AIR

When a person who is sick with TB and is not on treatment coughs or sneezes, TB germs are spread into the air.

These germs are breathed in by other people, especially those that are close by. The TB germs go into their lungs. The lungs are the part of the body that help us to breathe.

Anyone can be infected with TB.



Turn to Flipchart page 3

3 INFECTION

When the TB germ is breathed in it goes to the lungs and lies there hiding. Our immune system (body defense) sees that a new enemy has come into the body and quickly builds a fence around the TB germ to keep it from spreading. The TB germs lie there sleeping.

While the TB germ is sleeping the person will not feel sick and will look healthy. This is called TB infection.

Turn to Flipchart page 4

4 TB DISEASE

When the immune system gets weak, the TB germ is able to break through the fence and spread.

This is when the person will feel sick and show signs of TB. This is called TB disease.

Turn to Flipchart page 5

5 SIGNS OF TB

Do you know any of the signs that someone might have TB?
(ask the participant/s and wait for their answer)

The common symptoms of TB are:

- Cough that lasts more than 2 weeks
- Coughing up blood
- Fever
- Sweating at night (night sweats) even when cold weather
- Weight loss
- Feeling very tired all of the time
- Children will stop playing and will lose appetite

It is very important that anyone showing these signs comes for testing early to check if it is TB or something else. When people go for testing and treatment when they are already very sick there is risk that it will be too late for the medicines to be able to do their job in killing the TB.

If you see someone showing these signs please assist them to go for testing straight away.

6

Turn to Flipchart page 6

TESTING AND TREATMENT

TB testing is free and is done at the blue house at the hospital. The health care workers will help you with testing of sputum and an xray if needed.

If the results show TB then treatment is started. The medicines are taken daily for between 6-24 months depending on the type and strength of the TB.

If the TB is found early and treatment is taken every day then the TB germs will be killed and the person will be cured.

In Daru treatment is free and is given at treatment sites across the island.

7

Turn to Flipchart page 7

TB IN DARU

Daru has some of the highest rates of TB in PNG. The TB program in Daru is very strong and people are being cured every day. Last year 443 people completed treatment- this is a great success! But many people are still getting sick with TB each day.

The only way that we will be able to reduce TB for good in Daru is if there is widespread testing and treatment for both TB sickness AND sleeping TB.

Another island wide screening is planned soon to do this. I encourage us all to get our families checked and put on treatment when the screening happens.

8

Turn to Flipchart page 8

PROTECTING FAMILY

Remember that TB spreads through the air. So you can protect you and your family by:

- Opening windows and doors to let fresh air to blow TB germs out and allow sunlight in! Sunlight kills the TB germs.
- Avoiding overcrowded places and socialise outdoors when possible.
- Support and encourage any friends and family on TB medication to keep taking their treatment.
- Eat healthy food to keep your immune system strong.

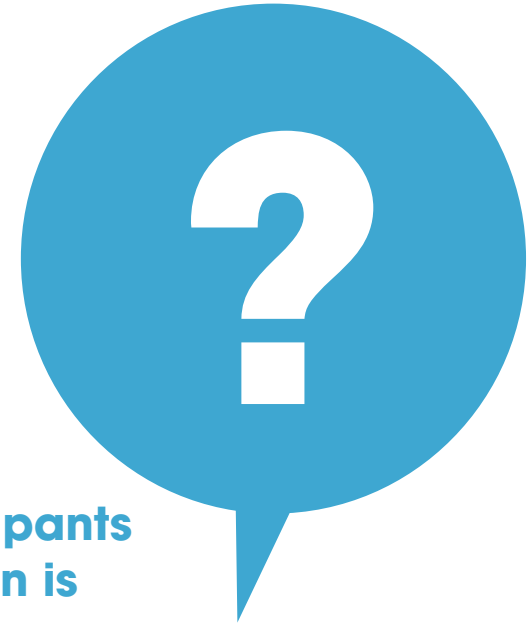
9

Turn to Flipchart page 9

3 THINGS TO REMEMBER

1. If TB is found early and treatment is completed, the TB germs will be killed and the person will be cured.
2. Follow the steps to protect you and your family and encourage anyone showing signs to go early for testing.
3. Make use of the screening when it comes to check if you and your family have TB.

Common Questions about TB



These are questions that the participants may ask about TB. Some information is given to help you answer.

Question: **Where did TB come from?**

Answer: TB has been around for thousands and thousands of years. TB germs have been found in Egyptian mummies and it is thought that there is some reference to TB sickness in the bible. It has been passed through humans from those times to today.

Question: **How did TB come to Daru?**

Answer: TB has been in Daru for many, many years. At some point in time, someone who was infected and became sick with TB in another place came to Daru. From there the germs spread to other people in Daru. Because Daru is a small island and most people live close together the germ has spread to many people.

Question: **Is TB caused by sorcery?**

Answer: No. TB is a medical sickness just like other sicknesses like malaria and the flu. It is caused by a germ that spreads through the air. TB has been around since ancient times (before the bible) and is in many countries around the world.

Common Questions about TB

Question: **Can TB be cured with herbs?**

Answer: No. The only thing that can cure TB is TB medicines. Just like malaria medicines cure malaria and typhoid medicines cure typhoid.

Question: **What makes the immune system get weak?**

Answer: There are many things that can weaken the immune system. Some common ones are:

- Sicknesses, for example diarrhoea, HIV, leprosy
- Malnutrition - this means not getting the right type, or enough food, that the body needs.
- Pregnancy - during pregnancy the immune system changes to allow the baby to grow.
- Overusing alcohol and drugs

Question: **Can TB be spread through sharing cups, plates or utensils? Or by shaking hands?**

Answer: No. TB is spread through the air. It can not be shared through contact with skin or by sharing items or clothing.

If you don't feel sure of the answer to a question that is asked, don't guess! Explain that you will check the answer and get back to them.

Your TB team support person will be there to assist with questions if you need.

Awareness session information

Please fill out this information every time you do an awareness session and share it with your TB team support person.

Day	Time	Participant Group	No. of Participants (M/F)

Awia esso roro gido.

Thank you for doing your part to Sweep TB out of Daru for good!

WESTERN PROVINCIAL HEALTH AUTHORITY
"COMMITTED TO SERVE"
WESTERN PROVINCE

Appendix 7.4: SWEEP-TB Data Safety Monitoring Committee: Terms of Reference

SWEEP-TB Daru

Systematic Community-Wide Engagement & Elimination Project for TB in Daru, Western Province, Papua New Guinea

TERMS OF REFERENCE AND FUNCTION
DATA SAFETY MONITORING COMMITTEE (DSMC)

Updated August 6, 2024

BACKGROUND:

The SWEEP- TB Daru project proposes to implement and evaluate an innovative tool to reduce the incidence of TB and MDR-TB on Daru, as part of a comprehensive package of interventions, and thereby reduce ongoing transmission and community prevalence. This "tool" is a TB preventive treatment (TPT) regimen that will treat TB infection in an individual by either or both rifampicin-susceptible or rifampicin-resistant strains of *Mycobacterium tuberculosis*. The regimen proposed is 6HLfx: 6 months of daily isoniazid and levofloxacin. This regimen will be offered to older children, adolescents, and young adults (5-34 years of age) who: do have active TB following clinical evaluation, CXR and sputum testing; do have evidence of TB infection indicated by a positive tuberculin skin test; have agreed to participate in the study; and have provided informed consent to take the regimen.

While there is extensive experience with both drugs in children, adolescents, and adults, especially in the treatment of TB disease, this regimen is novel as TB preventive treatment. Therefore, it will be important to monitor, evaluate and categorise all adverse events (potentially drug-related or otherwise) among individuals receiving this regimen as well as the drug-resistant profile of any incident active TB cases that occur at follow-up, either while receiving the regimen or during the post-treatment follow-up. Though there is no control group for direct comparison in this study population, it will be important to have independent monitoring of observational data that relates to individual and public health safety.

TERMS OF REFERENCE:

The DSMC will function as an independent advisory group.

The DSMC will specifically monitor:

1. Study recruitment, completion of study procedures and appropriate TPT initiation,
2. The frequency, severity and outcomes of adverse events that occur in study participants receiving TB preventive treatment (TPT),
3. Reporting of all serious adverse events to the relevant authorities within the specified time period, according to the specified reporting pathway (Figure 1),
4. Number and characteristics (age, drug-resistance) of incident TB cases that occurs amongst those who initiate TPT.
5. Linkage of TB patients (with prevalent or incident disease) to appropriate TB treatment and care.

The DSMC reviews 6 monthly study reports and may request additional interim data in order to clarify concerns or determine any emerging risks.

The DSMC will report to the Western Province PHA, the National TB Program (NTP), the Medical Research Advisory Committee (MRAC), The Pharmaceutical Services Standards Branch (PSSB) via the co-ordinating principal study investigator.

The DSMC does not have the authority to stop the study or modify the protocol. The DSMC findings and reports will be used to inform decisions by the study investigators in consultation with partners and authorities (above) who receive the reports as to whether to continue or suspend the study, or to amend the protocol.

The DSMC must protect the confidentiality of the study data and findings. The DSMC will have 4 members and include experts in clinical medicine and epidemiology / clinical trials /drug safety, with 2 experts from PNG and 2 international experts.

The specific roles and responsibilities of DSMC members are:

- To understand the research protocol and the plans therein for data and drug safety monitoring.
- To review interim reports, including details of all adverse events experienced by participants taking TPT, diagnosis and drug resistance profiles of incident TB cases and linkage to appropriate care of all prevalent and incident TB cases.
- If there are safety or data quality concerns, the DSMC can request further information from the study PI.
- To inform the study PI of any concerns regarding individual or public health safety, or study completion.
- To advise on any protocol modifications to improve study safety or feasibility.

- Provide advice and report back following meetings to the co-ordinating PI, as a consensus position via the DSMC chair. The chair will approve the meeting minutes (drafted by the secretariat and including a short progress summary) within 2 weeks of the DSMC meeting,

MEMBERSHIP

The DSMC will have 4 members and include experts from the Asia-Pacific region, with 2 from PNG, all with expertise in the management of TB and MDR-TB. One member will be appointed as the chair.

At least one member will represent: previous clinical or research experience in PNG; experience with managing children and adolescents with TB; TB-related DSMC experience.

The secretariat will be the study coordinator /project manager or delegate from the Burnet Institute.

OPERATING PROCEDURES:

- A DSMC meeting will have quorum with 3 members in attendance.
- Meetings will be held via teleconference / videoconference and arranged by the secretariat.
- The study investigators will produce a detailed interim analysis providing updates on study recruitment and addressing all key monitoring aspects, which will be sent to each member of the committee at least 1 week before the meeting date.
- Meta-data in the interim analysis will be provided in an aggregate form, and any patient level data will be provided in a de-identified manner.
- The principal investigator (PI) and other interested study investigators will attend as informants and observers but will be excused from the confidential DSMC discussions.
- The severity of AEs will be graded by the using the Division of AIDS table for grading the severity of adult and paediatric AEs (DAIDS) standard table as recommended by WHO and in the PNG PMDT SOP for the use of new and repurposed TB drugs
- The DSMC will strive to achieve consensus, but if necessary, a vote may be cast to assess (and record) the majority opinion.
- The chair will provide direct feedback to the PI (and relevant study investigators) at the DSMC meeting (after conclusion of confidential discussions), and in the meeting minutes/report.
- The secretariat will take minutes and provide them to the chair for review within 1 week of the DSMC meeting.

Appendix 7.5: Participant information and consent forms and education materials

Systematic Island-Wide Engagement & Elimination Project for TB in Daru, Western Province, Papua New Guinea (SWEEP-TB)

KO'OMIRITI TB

PARTICIPANT INFORMATION SHEET

Part 1: Detect and Treat TB in Daru

Why is the project being done?

The TB program in Daru is very strong but many people are still getting sick with TB each day. Research has shown that there is a high level of TB in the households and community in Daru.

The only way to reduce TB for good in Daru is through **widespread testing and treatment** for both **TB sickness AND sleeping TB**. The SWEEP-TB, or Ko'omiriti TB, island wide screening is doing exactly that.

Project description

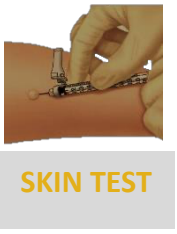
The SWEEP-TB project is visiting homes in Daru, PNG, **offering testing and treatment** for both TB sickness and Sleeping TB in residents.
It has the aim of **reducing the very high levels of TB** in the community.

What is involved?

Households will be offered screening for TB symptoms and testing at a mobile clinic in the community.

Everyone above the age of 10 will be offered a chest x-ray.

Other tests may include:



The team will ask you to return for review once results are ready and will support anyone who needs to start treatment for TB disease and will offer treatment to anyone up to 35 years old who has Sleeping TB.

Who is running the project?

The project is run by a team of staff from the Western Provincial Health Authority (WPHA), South Fly District Health, Burnet Institute and World Vision, with research support from the Papua New Guinea Institute of Medical Research and University of Papua New Guinea.

This study has been approved by the PNG Institute of Medical Research and the Medical Research Advisory Committee, National Department of Health, and the Alfred Hospital Ethics Committee in Melbourne, Australia.

Burnet World Vision The UNIVERSITY OF PAPUA NEW GUINEA PAPUA NEW GUINEA INSTITUTE OF MEDICAL RESEARCH National Department of Health

What are the risks?

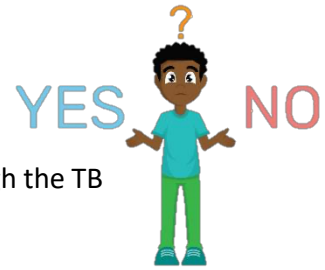
There are no risks that are different to standard medical care provided by the TB program in Daru.
No samples from your body (sputum) will be stored by the project or used later.

What are the benefits?

- You may be diagnosed with TB that you din't know about, which means a lower chance of getting very sick and lower chance of TB spreading to others.
- You will receive education on signs and symptoms of TB disease.
- It is expected that the project will reduce the number of people who become sick with TB in Daru.
- You will receive a free general health screening at your home and referral to hospital if needed.
- Food vouchers will be provided on completion of screening as appreciation for your participation.

Do I have to take part in the project?

No. Taking part in this project is voluntary- you do not need to take part if you do not want to. If you say yes now and then later decide to pull out, that is also ok.



If you decide not to take part in this project, you will still receive standard TB care through the TB program.

Confidentiality and your information

SWEEP-TB is being done through operational research. This means that information from the screening will be collected to help strengthen TB care in Daru and across PNG and the world. All information is part of the routine TB program in Daru led by the PHA. Your personal information will not be shared with anyone outside of the project team or staff providing health care to you.

The data, with names removed, will be accessed by the study team which includes researchers based in PNG and Australia. Other researchers may request access to the data without names. They will need ethics approval and approval of the SWEEP- TB research team.

What is the cost of taking part in the project?

There is no cost. All TB testing and treatment is free of charge.

Will I get paid for taking part in the project?

A 20 kina food voucher will be provided as a token of appreciation for the time taken to complete the screening process.

How do I find out the results of this project?

Workshops will be held during and at the end of the project where we will share the results with the community and provide information sheets.

What if I need further information about the project or have a problem?

Please feel free to ask any of the SWEEP-TB staff or Burnet Institute Program Team Lead (**Dr Tafireyi Marukutira)** at the Burnet Institute office, email: **tafireyi.marukutira@burnet.edu.au** or telephone: **75636185**.
Anyone with concerns or complaints about the conduct of the project can contact:
Gabriel Kama at the PHA office in Daru by email: **gabrielkama1978@gmail.com** or telephone **71508697**.

Or the complaints officer at the Alfred Hospital Ethics Committee, Melbourne, Australia by email: **research@alfred.org.au**

Together we can SWEEP TB out of Daru for good! Himara imehe go TB ko'omiriti Daru rudo! Yumi bung wantaim na rausim TB long Daru!

Systematic Island-Wide Engagement & Elimination Project for TB in Daru, Western Province, Papua New Guinea (SWEEP-TB)

Capacity to consent part 1 (detect and treat)

Instructions to research staff

- Ask the participant whether the following statements are true or false
- If the participant answers incorrectly, discuss the correct information, referring back to the participant information flipchart and form, before asking the same question again.
- If the participant is unable to questions on the 2nd try, this shows that they need a support person to assist them to provide consent

1. This project is about reducing the spread of TB in Daru

   True or False [Correct answer: True]

2. The health workers will ask you if you have any signs of TB

   True or False [Correct answer: True]

3. Tests will be done at a location in your community

   True or False [Correct answer: True]

4. Tests may include xray and giving sputum (kose opi)

   True or False [Correct answer: True]

5. You will need to pay for some of the TB tests

   True or False [Correct answer: False]

6. You have no choice, you have to take part in the SWEEP-TB project

   True or False [Correct answer: False]

7. The project team will not share private information about you with other people outside of the SWEEP-TB project team

   True or False [Correct answer: True]

8. You will receive a food voucher (20 kina) when you complete the screening and testing

   True or False [Correct answer: True]

9. You can pull out from the project at any time

True or False [Correct answer: True]

10. If you want to find out more information about the SWEEP-TB project at any time, you can ask the project staff.

    True or False [Correct answer: True]

Systematic Island-Wide Engagement & Elimination Project for TB in Daru, Western Province, Papua New Guinea (SWEEP-TB)

Capacity to consent part 2 (prevent)

Instructions to research staff

- Ask the participant whether the following statements are true or false
- If the participant answers incorrectly, discuss the correct information, referring back to the participant information flipchart and form, before asking the same question again.
- If the participant is unable to questions on the 2nd try, this shows that they need a support person to assist them to provide consent

1. The SWEEP-TB project wants to help me to find out if I have Sleeping TB

True or False [Correct answer: True]

2. The skin test shows if someone has Sleeping TB

True or False [Correct answer: True]

3. There is no treatment for Sleeping TB

True or False [Correct answer: False]

4. Anyone under 35 who has Sleeping TB will be offered treatment

True or False [Correct answer: True]

5. The project team will take out personal information, such as names, before sharing information about the project

True or False [Correct answer: False]

6. Anyone who completes Sleeping TB treatment as part of the project will receive a food voucher

True or False [Correct answer: True]

7. If you pull out from the project later you will still be able to receive the usual TB care and services

True or False [Correct answer: True]

8. If you want to find out more information about the SWEEP-TB project at any time, you can ask the project staff.

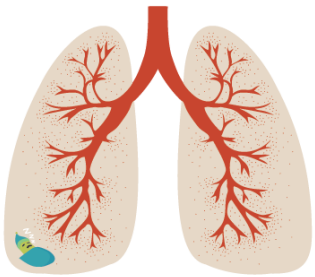
True or False [Correct answer: True]

Systematic Island-Wide Engagement & Elimination Project for TB in Daru, Western Province, Papua New Guinea (SWEEP-TB)

PARTICIPANT INFORMATION SHEET

Part 2: Prevent TB in Daru

Why we want to prevent TB disease

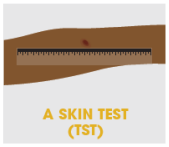


To SWEEP TB out of Daru for good, we have to treat TB Disease **and** Sleeping TB. At the moment, there are no guidelines in PNG about how to treat Sleeping TB in people who have been in contact with the stronger type of TB, called MDR-TB. The SWEEP-TB project is offering treatment for Sleeping TB and TB vaccination for more people in Daru up to the age of 34 to reduce their chance of getting sick with TB disease and reduce the spread of TB in the community.

Project description:

The SWEEP-TB project is visiting homes in Daru, PNG, offering **testing, treatment and prevention** of tuberculosis (TB) in residents. It has the aim of reducing the very high levels of TB in the community.

This part of the SWEEP-TB project is offering testing and treatment for Sleeping TB and the vaccination for TB, called BCG, for more people who live in Daru.



What is involved?

Step 1: Finding out if you have Sleeping TB

A TB nurse will do a **skin test** to find out if you have Sleeping TB. This test (called TST) involves a small injection into the skin of your arm. After 2 days, a healthcare worker from the project will check the skin reaction (bump). The size of the bump will tell us if you have Sleeping TB or not. **After a few days, the bump will go away by itself**.

Step 2: Treating Sleeping TB

Children, teenagers and young adults under 35 years who do not have symptoms of TB disease and have Sleeping TB will be offered treatment. The type and length of treatment will depend on age and whether the person has been in contact with someone with drug sensitive TB (DS-TB) or multi drug resistant TB (MDR-TB).

The SWEEP-TB team will give you the medicine, and will show you how to prepare the medicine if it is for your child. Each month, you will be asked to attend a DART site for review and supply of medicine. Counsellors will provide education and support to you.

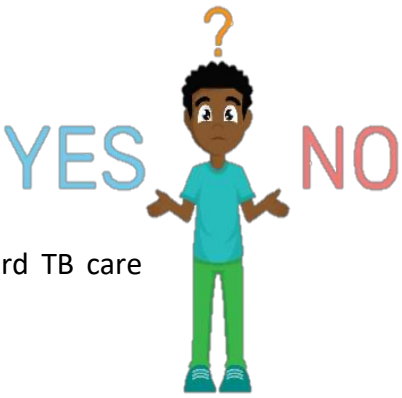
Burnet World Vision The University of Papua New Guinea PNGIMR Papua New Guinea Institute of Medical Research National Department of Health

Vaccination
If you are under 35, have a negative TST and have not had the BCG vaccine, you will be offered the vaccine.

Step 3: Follow up
When you complete treatment for Sleeping TB, you will be asked to attend for a check **every 6 months for 2 years** to make sure there are no symptoms of TB disease. You are encouraged to contact the project staff at any time if you have questions or concerns.

COMMON QUESTIONS

Do I have to take part?
No. Taking part in this project is voluntary- you do not need to take part if you do not want to. If you say yes now and then later decide to pull out, that is also ok.



If you decide not to take part in this project, you will still receive standard TB care through the TB program.

Cost of taking part in the project?
There is no cost. All TB testing and treatment is free of charge.

Benefits of taking part in the project?
- If you or your child receive treatment for Sleeping TB, it will lower the chance of getting sick with TB disease and spreading it to others.
- A 60 kina food voucher will be provided on completion of Sleeping TB treatment.

What are the risks in participating?
Side effects are a reaction to medication. Like any other medicine, the Sleeping TB medicine can cause side effects. **Most people feel fine** when taking the medicine and don't have any side effects.

It is possible you or your child may experience:
- A rash
- Stomach upset, nausea, vomiting or diarrhea (pek pek wara)
- Headache, dizziness, trouble sleeping, shakes

There is a team of experts who check the safety of the project. A health worker will provide more education on the side effects when starting the medicine and the doctor can stop the medicine if needed during your treatment.

You may feel a small amount of pain from the TST injection. It is possible that there may be a skin rash or bruising. It's very rare that a scar may come up where you are injected. If you experience these or any other symptoms, please let the project team know.

What information will be collected?
If you choose to take part in this project, we will collect some information such as **age, gender, address, weight at follow-up visits, and any side effects**. You will have full access to this information. You also have the right to request that any information that you disagree with be corrected.

How will your information be used and kept confidential?
SWEEP-TB is being done through operational research. This means that information from the screening will be collected to help strengthen TB care in Daru and across PNG and the world. All information is part of the routine TB program in Daru led by the PHA. Your personal information will not be shared with anyone outside of the project team or staff providing health care to you.

The data, with names removed, will be accessed by the study team which includes researchers based in PNG and Australia. Other researchers may request access to the data without names. They will need ethics approval and approval of the SWEEP- TB research team.

How do I find out the results of this project?

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Together we can SWEEP TB out of Daru for good! Himara imehe go TB ko'omiriti Daru rudo! Yumi bung wantaim na rausim TB long Daru!

SWEEP ID:

Consent Form

Adult providing own consent or Carer / Guardian for child or adult who is unable to consent

Project Title	**Systematic Island-Wide Engagement & Elimination Project for TB in Daru, Western Province, Papua New Guinea (SWEEP-TB)**
Principal Investigators	Dr Niko Wuatai, A/Prof Suman Majumdar
Site Investigators	Mr Gabriel Kama, Dr Tafireyi Marukutira
Location	Daru, South Fly District, Western Province, Papua New Guinea

Assessment by study team member/researcher

Is the participant able to provide consent? **Y ☐ / N ☐**

If N, is a parent/guardian/support person able to provide consent? **Y ☐ / N ☐**

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand what the activities and risks of the project are.

I give permission for my health information to be shared with the Burnet Institute and Western Provincial Health Authority for the purposes of this project. I understand that the **information will be kept confidential.**

I have had an opportunity to ask questions and I am satisfied with the answers I received.

I / my child/person I am supporting, **freely agree to participate** in this research project as described. I understand that if I pull out of the study, **I will still be able to access usual TB care** through the TB program. My medical records may be **used for follow-up.**

Name of Participant (please print)
_____
Name of parent / guardian if child or unable to sign
_____
Signature _____ Date_____

Name of Witness* to Participant's Signature (please print)
_____
Signature _____ Date_____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study team member / researcher[†]

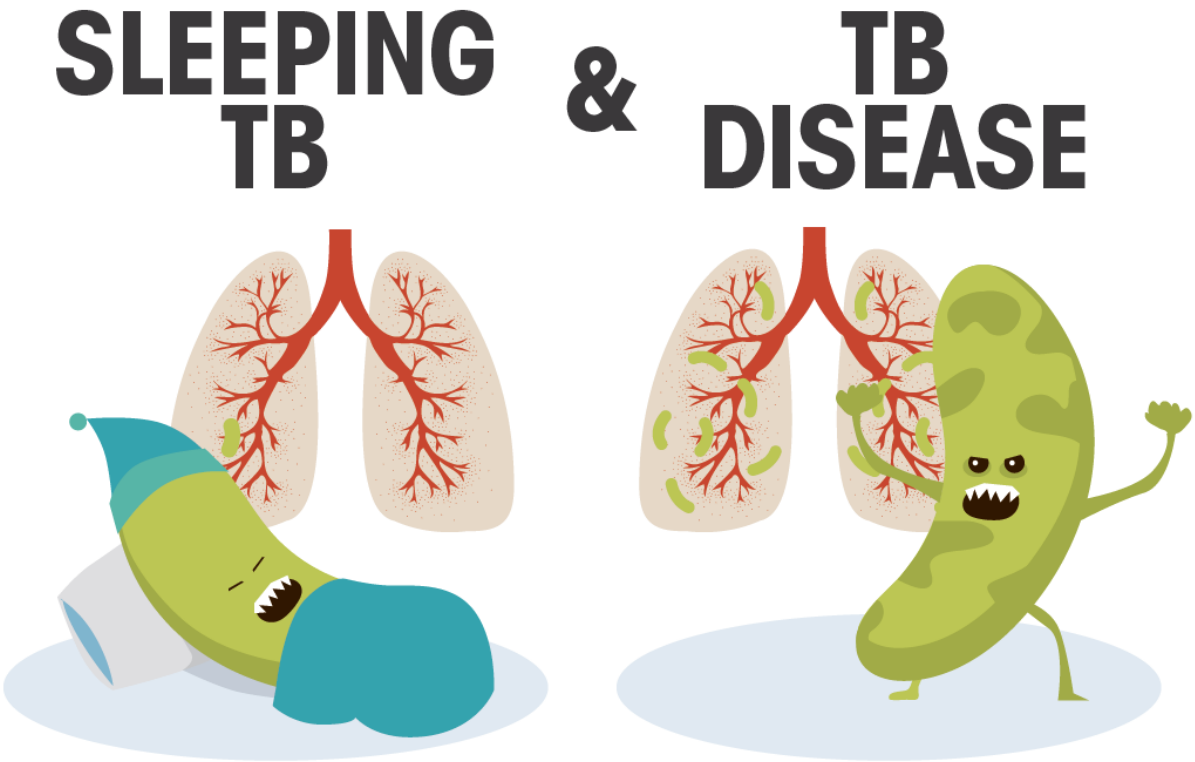
I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of study team member (please print)
_____
Signature _____ Date_____

[†] A member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature

SWEEP-TB Daru
TB Ko'omiriti



Burnet

World Vision

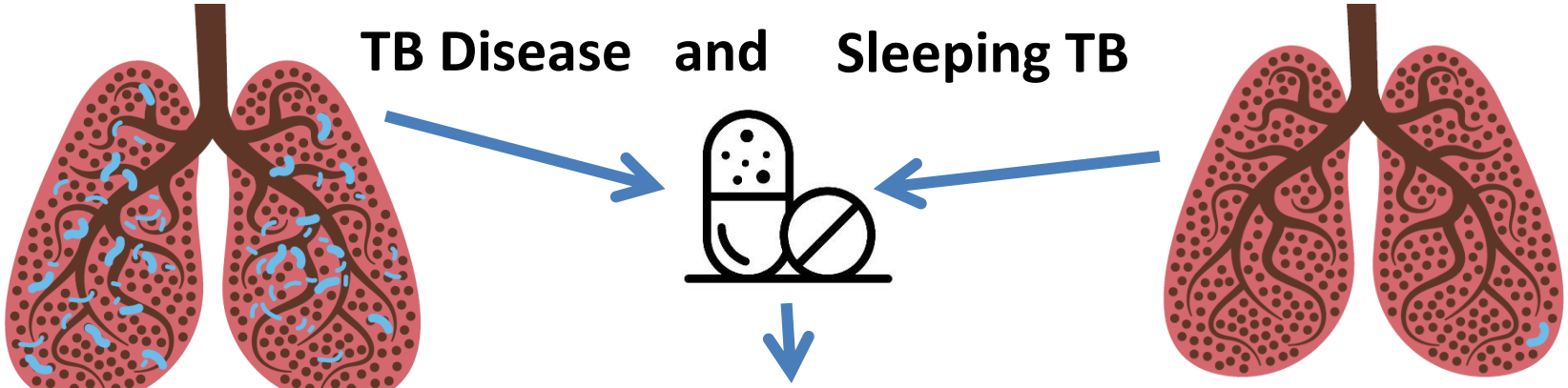
Screening visit

You, and your family, are being invited to take part in this project

Why is the project being done?

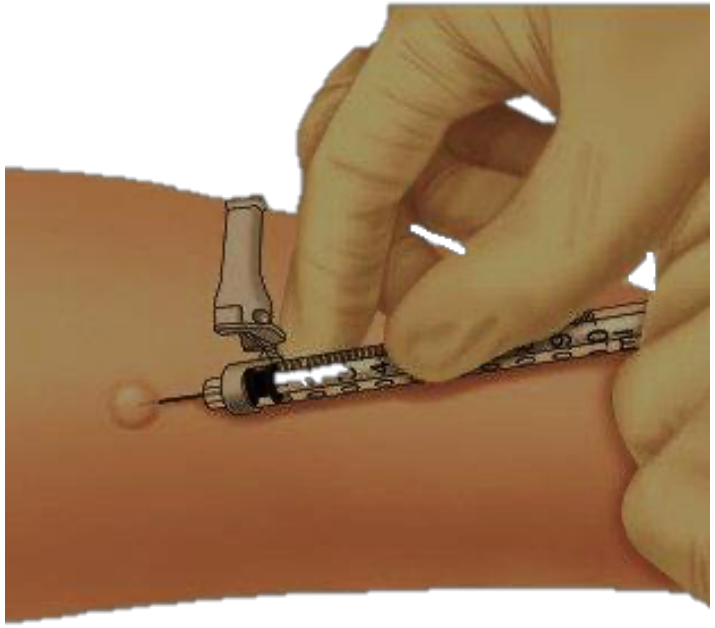
To SWEEP TB out of Daru for good, we have to treat

TB Disease and Sleeping TB



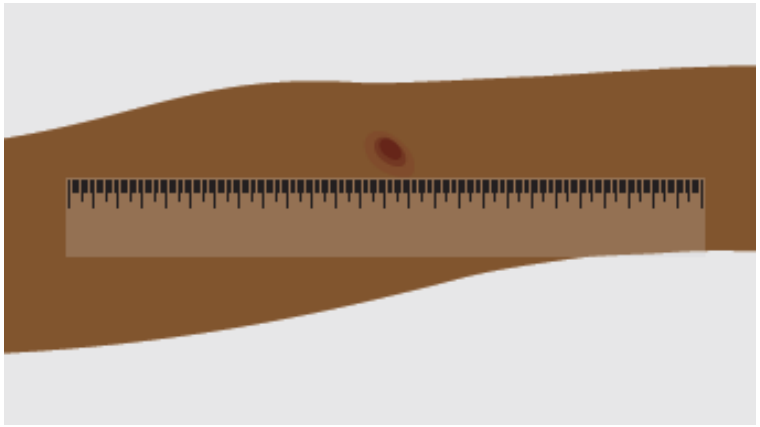
What is involved?

Step 1 **Finding out if you have Sleeping TB**



A skin test, called TST, checks if you have Sleeping TB

After 2 days a health care worker will check your skin reaction (bump)



The bump will go down after a few days

What is involved?

Step 2
(under 35)

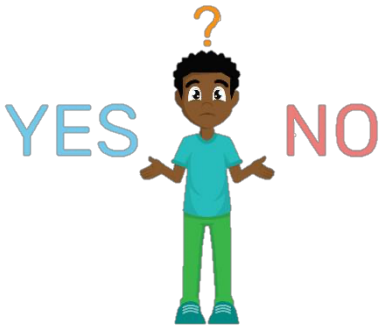
Treatment for Sleeping TB

Step 3

Follow up

BCG- TB vaccine

Things to remember from information sheet 1



It is your choice whether you take part

There is no cost to take part

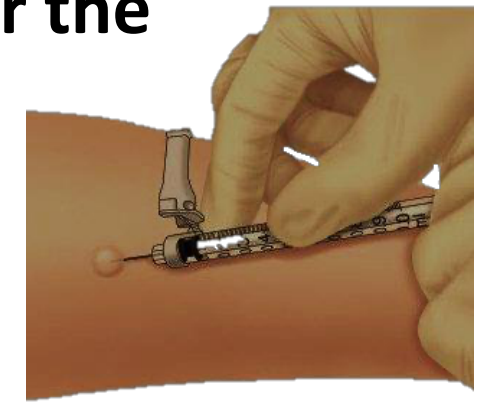
Your personal information will not be shared

There will be workshops to give updates

You can ask staff if you would like more information

Do you have any questions about this information?

Remember that consent is for the skin test for Sleeping TB



And treatment for Sleeping TB if the skin test result is positive