Epidemiological Profile of Tuberculosis Patients from the Torres Strait Islands, Including Visitors from Papua New Guinea to the Torres Strait Protected Zone

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in fulfilment of the requirements for the degree of

Doctor of Philosophy

Townsville, October 2023

Declaration of Originality

I declare that this thesis is my own work and has not been submitted in any form for another degree or diploma at any university or other institution of tertiary education.

Information derived from the published or unpublished work of others has been acknowledged in the text and a list of references is given.

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J'Belle Foster

9 October 2023

Declaration on Ethics

The research presented and reported in this thesis was conducted with the approval of the Far North Queensland Human Research Ethics Committee, James Cook University Research Ethics Committee and in accordance with National Statement on Ethics Conduct in Human Research, 2007.

J'Belle Foster

9 October, 2023

Statement of Access

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J'Belle Foster

9 October, 2023

Acknowledgements

Words fall short of my immense gratitude to you, Professor Emma McBryde, for your guidance and support, and for helping me to pursue this research. Without your time, wisdom, and knowledge, I would not have made it this far. I am in awe of how you managed to so beautifully navigate the path of being both my colleague and my primary supervisor. I am incredibly grateful that you were there the whole time, working alongside me and bearing witness to the tragedies and the successes of managing TB at the international border. I truly appreciate your enthusiasm for research and for the safe space you built around me which allowed me to find and refine each line of inquiry.

To Dr Diana Mendez, my Doctoral Cohort mentor and later, my secondary supervisor, ten thousand blessings to you. You were there from the start and you had a front row seat to every struggle. Thank you for your patience and for your friendship, and of course, for that infamous red pen.

To Professor Ben Marais, words cannot adequately express my appreciation for your guidance. I feel incredibly fortunate to have had you as my external mentor – you are a maestro among TB experts and a defender of children with TB. Your insights and experiences have further cultivated a desire in me to use evidence to strive for hope in change.

To Dr Dunstan Peniyamina, my colleague, cultural mentor and dear friend, I am so grateful to you for so many things – for your insights, experiences, stories, review of manuscripts, for saving me a seat next to you Cross Border Health Issues Committee meetings, for your ability to say a thousand words to me about cross border health care with just one smile. Dr Peniyamina, thank you for caring so deeply about the plight of patients at the Torres Strait / Papua New Guinea (PNG) border.

To my colleagues Adana Maza, Rotona Martin and Jared Noah, from the Cross Border Data Integrity Project and the Torres and Cape TB Control Unit, thank you for your dedication, commitment and passion for TB control. So many of the successes described in this thesis were as a direct result of your unfailing efforts in the TB Control Unit, and the level of detail I was able to provide would not have been possible without your work on the Cross Border Data Integrity Project. Mina Big Esso!

To Dr Chris Coulter and Dr Justin Denholm, thank you for the tremendous support you each provided, that seemed to arrive at the times it was most needed. I am so grateful that you both intuitively understood the sensitivities of the data and helped me to find a path to reconciliation with it as a clinician.

To Dr Oscar Whitehead, tusind tak for at ændre retningen på mit liv. Tak for din urokkelige dedikation til at forbedre velbefindendet for patienter i Torres Strædet / Papua Ny Guinea grænseregionen. De liv, du berører, er utvivlsomt bedre pa grund af dine bestræbelser.

Thank you to Cheryl and Michael Oats, for your love and support and for opening your home to me each time I needed to visit the Townsville campus.

To my parents, thank you for opening your home to me during writing retreats and for the endless cups of tea, delicious meals, and words of encouragement. Thank you, Dad for being my layman and reading my articles. You harness the English language like no one else I have ever met and throughout this process, I have strived to channel the talent in the bloodline. To my siblings, thank you for your encouragement over the years.

To my husband, without your love and support I would not have been able to complete my studies. Thank you for being my sound board when I needed it, and especially, thank you for the gift of time to complete. Jeg elsker dig altid.

Situating the Research

While undertaking my Master of Public Health / Master of International Public Health, I secured an internship in Nepal with the Nepal Red Cross Society (NRCS) and with a non-Government organisation, All Nepal Public Care Society (ANPCS). With NRCS, my tasks varied from travelling to remote communities to provide education and training to NRCS community volunteers about influenza and closed defecation practices, to writing funding grant applications to assisting with natural disaster (earthquake) simulations. Little did I know at the time, but it was my work with ANPCS that would profoundly change the direction of my life. ANPCS is based in Anamnagar, Kathmandu, and while the shopfront (and main source of income) is a pharmacy and primary health clinic, other services offered were mass vaccination programs, remote area outreach camps to disadvantaged communities, a Sexually Transmissible Infection / Human Immunodeficiency Virus (HIV) clinic, a leprosy clinic and a Directly Observed Therapy centre for tuberculosis (TB) patients. The Director of ANPCS,

Bhakta Bahadur K.C. dedicated his life to helping those less fortunate and became my most cherished mentor and friend. From the ladies that trekked down the mountain each day to sell vegetables outside the clinic, to each and every customer and patient, Bhakta treated them all as family. We shared seemingly endless cups of tea with customers and patients, but it was the tea we drank and the connections made with the TB patients after they had washed down their daily dose of anti-TB treatment, that truly solidified my desire to work in the field of infectious diseases.

It was not long before I secured employment on a World Health Organization-funded research project with Johns Hopkins University and the Tibetan Delek Hospital. This project was based in the foothills of the Himalayas in India, and home to His Holiness the Dalai Lama. I worked as a research officer with Tibetan refugees on an active TB case finding study, specifically looking at multidrug-resistant (MDR)-TB in residents of Tibetan monasteries, nunneries, in Tibetan primary schools and in newly arrived Tibetan refugees from China. The largest proportion of the work was with children in the monasteries and schools; most of them were orphans who had been lovingly bundled up by their parents in Tibet under the cover of night and sent on a dangerous three-week trek with people smugglers into India. In the early days, what struck me the most was the lengths that these parents went to in order to enable a better life for their children, albeit knowing that they would likely never again have any contact with their children.

It was in India that I met Dr Kerry Dierberg, the second person who would shape my professional life and from whom I learned a great deal about the management of TB, the importance of accurate data and developing meaningful collaborations. Although Kerry was based in the United States for the majority of the research project with three or four site visits, we had near daily communication. I credit Kerry for preparing me to move beyond the boundaries of professional health care provision and teaching me the value of transformative learning. I credit too, the Tibetan nurses (Tsering Paldon, Dorjee Kunchok, Chemi Dolka) I worked with, and who taught me that duties and moral responsibilities can sit easily alongside sacred moments – that the quiet task of cradling and softly singing to a sick child or listening to a patient express their fears about their new MDR-TB diagnosis can be a universal proclamation of safety and peace and is just as important as any life-extending medical intervention.

In my darkest hours in India, when my own sense of safety and peace had seemingly escaped me and all I had were the memories of the day - the pale skin, protruding bones, and sunken eyes, I turned to Shakespeare and Keats. As my 'Ode to India', and in subtle and not so subtle ways, I have woven some words of these literary greats into my thesis and a publication, as a token of my appreciation for literary immortality and the comfort they bestowed.

One very distinct situation has remained with me from my time in India. During an outreach visit to one of the Tibetan boarding schools, I met a nine-year old child who had shared a dormitory room with five friends who had all died from TB in the previous two years, with no evidence whatsoever that he had been exposed to the mycobacterium. Rather than be concerned for himself in any way (and also convinced he had certain super-powers against TB), he volunteered to be my research assistant as his sole purpose in life had become ensuring no more of his friends ever perished from TB again. We spent many afternoons together labelling sputum specimen jars and he assisted further by convincing the younger children to come forward to be assessed, even though I know he was bribing some of the children with promises that they could touch my skin and hair! Once upon a time, in a small and remote Tibetan boarding school in India, my interest in paediatric TB was born.

Working with very limited resources or in extraordinarily challenging circumstances was something that gave me great satisfaction. In Nepal, it was how we ripped the end of a bandage lengthways and used it to wrap around an extremity and tie a knot at the end of a dressing as there was no tape. In India, there wasn't a postal system that could deliver our sputum specimens to the Tibetan Delek Hospital for processing. To strive for timely delivery of specimens from outreach clinics in remote settlements to the hospital-based laboratory in Dharamsala, the Tibetan nurses and I would find any bus heading to Dharamsala, identify Tibetan passengers based on their appearance alone, and with a letter in hand from his Holiness the Dalai Lama who was a patron of the research, requested that the passenger deliver the specimens to the Tibetan Delek Hospital. Not one specimen did not make it!

Another example of embracing scarce resources was in India prior to visiting patients in the MDR and extensively drug-resistant (XDR)-TB ward, or prior to a TB clinic when we needed to check that our masks were still effective. One at a time, the Tibetan nurses and I would don our masks, lock ourselves in a closet and light a stick of Tibetan prayer incense (the most potent incense on the planet). If after five minutes, you could smell the incense, your mask did not fit or was no longer working properly. If you could not smell it, the 'fit-test' was complete! We

would reuse our masks for weeks, only changing them if they got wet. We would get online and beg international travellers and student doctors to bring and donate N95 or P2 respirators to the Tibetan Delek Hospital. To go from this to throwing out N95s after every use in an Australian hospital was extremely difficult to come to terms with.

Toward the end of the contract in India, I secured what I imagined to be a rare opportunity to work in TB Control in Australia. Securing employment as the Clinical Nurse Consultant – Tuberculosis for the Queensland Department of Health, was my next step. Unbeknownst to me at the time, I had entered the TB Program at a time of turmoil, and right in the middle of a process of decentralisation that had threatened to shut down the TB centre in Brisbane. While I am proud to have established the Queensland TB Nurses Network which exists to this day, I realised fairly quickly that I missed working in TB with the population.

After 15 months working within the Queensland Department of Health, the Qld Chief Health Officer supported my move to the Torres Strait in 2014 to work on a federally funded cross border (Australia / PNG) TB project. The cross-border project was extended to 2016 and enabled me the opportunity to connect with a multitude of stakeholders in many communities, on both sides of the border. One of the initiatives of the cross-border TB project was to visit every Torres Strait Island and most PNG Treaty villages with the local Department of Foreign Affairs and Trade representative and provide an information session on TB in the region. I owe an enormous debt of gratitude to Mr Fraser Nai of Yorke Island who initially vetted my sessions prior to visiting community and over my seven years as a resident of Thursday Island, became a trusted friend and mentor. I am acutely aware and appreciative of Fraser, for without his careful and considerate explanations of cultural concepts that he so beautifully weaves into every-day conversation, my experiences living in community on Thursday Island, would not have been as meaningful. I was also extremely fortunate to have crossed paths with Salee Salee, wife of Kebei Salee from Sigabadaru, PNG, who was initially assigned to remain with me during village visits to assist with TB educations sessions for women and children, but who would later become my cultural mentor and close companion during my many visits to Saibai Island.

I discovered a lot of gaps in TB service delivery during the cross-border TB project, and in early 2015, I wrote the business proposal and secured funding to establish the Torres and Cape Tuberculosis Control Unit. The Torres and Cape TB Control Unit was officially established on January 4, 2016. My experiences in the Torres Strait, my connections with PNG neighbours

and stakeholders, convinced me that the locally-based TB program needed to be amenable to the needs of both residents of the Torres Strait and PNG nationals, with sufficient flexibility to ensure both rapid response to issues of public health concern and an ethos that supported continual quality improvement initiatives. As the Nursing Director of the Torres and Cape TB Control Unit, as well as the individual that established it, I recognise that I am extremely close to the topic and data included in this thesis. I have felt a deep sense of responsibility throughout the PhD process, to ensure that all my actions were for the purpose of programmatic improvement.

A key strength of the studies in this thesis, is the underpinning of innate programmatic knowledge of the inner workings of TB management and the familiarity with patients diagnosed from 2016. Working and researching in the same field involves navigating the invisible line between applied clinical care as an employee and clearly seeing the potential benefits to patients through translational research.[1] Without having local knowledge about processes and TB control efforts in the region, the depth of data collected and analyses performed, may have been limited. Examples include knowledge of which specimen collection modalities are available on each island (Chapter 2); which baseline measurements are collected and point of care testing used for patients with presumptive TB that may not automatically feed into an electronic patient databases (Chapter 3); where to look to find supplementary evidence such as onset of symptoms and poor outcomes for patients (Chapter 3); the level of communication and the changes to communication pathways over time between TB programs in Queensland and PNG (Chapter 4); the depths and practicality of local protocol implementation, stakeholder engagement and collaboration related to aeromedical retrievals of PNG nationals (Chapter 5); the level of knowledge of and adherence to local cross-border TB-related policies and procedures (Chapter 5); knowledge about what exactly PNG patients need to undergo to first present to an Australian health facility, what their journey involves when they are discharged back to the PNG health system (Chapter 1) and knowledge of and relationships with many of the stakeholders in the region (Chapters 1 to 6).

Hence, the primary purpose for pursuing this PhD, was to use evidence to support grass-roots improvements at the local level in the Torres and Cape TB Control Unit. In the same way that every decision made all those years ago, was for the sole purpose of inching ever closer to working as a nurse in low-and-middle-income countries, so too was my intention to carefully select studies for this PhD that would enable the most significant changes in TB control in the

Torres Strait. Rather than generating evidence for future change, this PhD has enabled me to implement true translational research, based on real-time, and locally-derived evidence. Research findings derived from this PhD have provided an evidence-based understanding that has supported demonstrable programmatic improvements to TB services delivered in the Torres Strait region. By contributing to conceptual and methodological understandings, we have the potential to influence health care provision, policy, and practice for TB services in the Torres Strait.

Statement on the Contributions of Others

Preamble. Summary

Feedback from my supervisory team was requested and edits and suggestions were implemented.

Chapter 1. Scoping Reviews

Dr Chris Coulter provided access to historic information about the Queensland Tuberculosis Control Centre and the diagnostic support provided by the Queensland Mycobacterium Reference Laboratory for specimens collected in the Western Province, PNG. Dr Diana Mendez proposed the data chart method to adequately capture details of the literature used within this chapter. Dr Dunstan Peniyamina provided specific feedback about health-related activities in the Treaty villages and on Daru Island and was my cultural advisor. Feedback from my supervisory team was requested, and edits and suggestions were implemented.

Chapter 2. Data Collection

Various nursing, Indigenous Health Worker and administration staff were gainfully employed to work on the Cross Border Data Integrity project which I managed from 2014 to 2016. Their dedication to the task has led to a greater level of detail in this research about patient care which would otherwise not have been available. I specifically requested Professor Emma McBryde to cross-check the information about the changes that were made to the classification of case notifications by the Communicable Diseases Branch in 2018. This is because Professor Emma McBryde was gainfully employed as a TB Specialist in the Torres and Cape Tuberculosis Control Unit at the time these changes were made. Feedback from my supervisory team was requested, and edits and suggestions were implemented.

Chapter 3. Diagnostic Yield

Professor Adrian Estermann provided advice on how best to organise the data in SPSS for analysis. Professor Emma McBryde and Professor Ben Marais contributed to the study design and interpretation of results. Professor Emma McBryde provided expert advice on chest x-ray interpretation. Statistics Solutions software was used for initial data analysis and then cross-

checked in SPSS. Feedback from my supervisory team and doctoral cohort mentor was requested, and edits and suggestions were implemented.

Contributions in Chapter 3

Chapter	Publication or Manuscript	Contribution of each author including the candidate
3	Foster, J., Marais, BJ., Martin, R., Peniyamina, D., Mendez, D., Warner, J., McBryde, ES. (2021). TB in the Torres Strait: The Lady Doth Test Too Much. Rural & Remote Health, 21 (1).	Conceptualisation, J.F.; methodology, J.F. and E.S.M.; investigation, J.F.; software, J.F.; formal analysis, J.F.; writing—original draft preparation, J.F., writing—review and editing, J.F., B.J.M., R.M., D.P., D.M., and E.S.M.; supervision, E.S.M., D.M. and B.J.M. All authors have read and agreed to the published version of the manuscript. Proportion of the work that I undertook: 90%.

Chapter 4. The Rise of Drug-Resistance

4.1. Mr Matthew Murray (Commonline Pty Ltd) mapped case notification data in geo-mapping software, Carti. Professor Emma McBryde suggested adding ethionamide-resistance in study 4.1. Feedback from my supervisory team and doctoral cohort mentor was requested, and edits and suggestions were implemented.

4.2. Professor Emma McBryde suggested we respond to the Baird et al. (2018) article. Subject matter expert for TB management on Daru Island, PNG Dr Maggie Taune co-authored Section 4.2 and Dr Dunstan Peniyamina provided feedback on the manuscript to ensure the wording and detail was culturally appropriate. Feedback from Professor Emma McBryde was requested, and edits and suggestions were implemented.

4.3 and 4.4. Professor Emma McBryde contributed to the study design and interpretation of results. Statistics Solutions software was used for initial data analysis and then cross-checked in SPSS in Sections 4.3 and 4.4 whereby SPSS was used for final analyses. Feedback from my supervisory team (at which point my doctoral cohort mentor became my secondary supervisor) was requested, and edits and suggestions were implemented.

Contributions in Chapter 4

Chapter	Publication or Manuscript	Contribution of each author including the candidate
4.1	Foster, JB., Mendez, D., Marais, BJ., Peniyamina, D., Murray, M., McBryde, ES. (In review). Spatiotemporal trends of drug-resistant TB in the Torres Strait Islands, Australia and Papua New Guinea border region between 2000 and 2020.	Conceptualisation, J.F.; methodology, J.F.; investigation, J.F.; software for data analysis, J.F.; software for geospatial mapping, M.M.; verifying location of Treaty villages, D.P.; formal analysis, J.F.; writing—original draft preparation, J.F., writing—review and editing, J.F., D.M., B.J.M., D.P. and E.S.M.; supervision, E.S.M., D.M. and B.J.M. All authors have read and agreed to the final version of the manuscript. Proportion of work that I undertook: 90%.
4.2	Foster, J., McBryde, ES., Taune, M., Peniyamina, D. (2018). Cross-border tuberculosis: opportunities, challenges and change. International Journal of Tuberculosis and Lung Disease, 22 (9), 1107-1108.	Conceptualisation, E.S.M., writing—original draft preparation, J.F. and E.S.M.; writing—review and editing, J.F., E.S.M., M.T. and D.P.; supervision, E.S.M. All authors have read and agreed to the published version of the manuscript. Proportion of work that I undertook: 70%.
4.3	Foster, JB., Mendez, D., Marais, BJ., Peniyamina, D., McBryde, ES. (2022). Time to commencement of effective treatment in patients with drug-resistant tuberculosis diagnosed in the Torres Strait/Papua New Guinea cross-border region. Rural Remote Health, 2023, 23 (1).	Conceptualisation, J.F. and E.S.M.; methodology, J.F. and E.S.M.; investigation, J.F.; software, J.F.; formal analysis, J.F.; writing—original draft preparation, J.F., writing—review and editing, J.F., D.M., B.J.M., D.P. and E.S.M.; supervision, E.S.M., D.M. and B.J.M. All authors have read and agreed to the final version of the manuscript. Proportion of work that I undertook: 85%.

Chapter	Publication or Manuscript	Contribution of each author including the candidate
4.4	Foster, JB., Mendez, D., Marais, BJ., Peniyamina, D., McBryde, ES. (2022). Predictors of unfavourable outcome in patients diagnosed with drug-resistant tuberculosis in the Torres Strait/Papua New Guinea border region. PLoS ONE, 17 (12), e0266436.	Conceptualisation, J.F. and E.S.M.; methodology, J.F. and E.S.M.; investigation, J.F.; software, J.F.; formal analysis, J.F.; writing—original draft preparation, J.F., writing—review and editing, J.F., D.M., B.J.M., D.P. and E.S.M.; supervision, E.S.M., D.M. and B.J.M. All authors have read and agreed to the published version accepted for publication. Proportion of work that I undertook: 85%.

Chapter 5. High Price

In the lead up to the development of this chapter, Torres and Cape TB Control Unit TB Specialist Daniel Judge suggested we undertake a cost analysis. Chapter 5 is comprised of two studies that were initially one larger study but where a decision was made to separate cost issues from patient management and ethical components of the study. Chapter 5 contains the only studies in this thesis whereby there was an overlap in my gainful employment in the Torres and Cape TB Control Unit and as a PhD Candidate. This was because there was an operational benefit to having accurate costings available as funding agreements with the Commonwealth Department of Health were due for renewal. An amendment to my Ethics approval to access additional data was obtained, with Site Specific Authorisation obtained from the data custodian who was also my line manager at the time. Financial data and process information was provided and supported by written approval from the Queensland Aeromedical Retrieval Disaster Management Branch (ARDMB) Research Committee, and Queensland Ambulance Service Torres and Cape York Local Ambulance Service Network (QAS). The Revenue Manager on Thursday Island provided advice and information on the unique sub-category of Medicare ineligibility and Reciprocal Health Care Agreements in relation to PNG Nationals accessing healthcare via the TSPZ. Feedback on the manuscript from my line manager, Torres and Cape Hospital and Health Service (TCHHS) Revenue Manager and Chief Finance Officer, ARDMS, QAS, co-authors, my supervisory team and doctoral cohort mentor was requested, and edits and suggestions were implemented.

In the interest of patient safety and transparency, midway through completing the audit described in Section 5.2, the TCHHS Executive Director of Medical Services (also the Chair of the TCHHS Clinical Governance Committee) was informed that the Child Early Warning tool used to detect deterioration in the region, was not effective at detecting deterioration in children presenting with signs and symptoms of TB. The TCHHS Director of Medical Services (North) and the TCHHS Executive Director of Nursing and Midwifery were also informed.

Upon recognition that the results of Section 5.2 had human rights implications, a TB Specialist and bioethicist was consulted and through this consultation, provided sufficient feedback to warrant an invitation to be co-author on the manuscript. Feedback from my supervisory team was requested, and edits and suggestions were implemented. Given the findings of this study were unexpected and the publication of them had the potential to bring reputational harm to the TCHHS, consultation followed with the Queensland Department of Health, Queensland Nurses and Midwives Union, TCHHS Research Governance Officer and TCHHS Chief Executive prior to submission for publication. Prior to submission for publication and per the James Cook University / TCHHS Research Agreement, the TCHHS Chief Executive was provided the opportunity to review and request amendments to the manuscript. Once satisfied with the content of the manuscript, the TCHHS Chief Executive provided a formal letter of acceptance (Appendix E). Upon publication, TCHHS Director of Clinical Governance, Director of Medical Services (North), TCHHS Research Governance, Far North Queensland Human Research Ethics Committee, TCHHS Chief Executive and the Principal Media Officer for Rural and Remote Queensland within the Queensland Department of Health were notified.

Contributions in Chapter 5

Chapter	Publication or Manuscript	Contribution of each author including the candidate
5.1	Foster, JB., Judge, D., Mendez, D., Marais, BJ., Peniyamina, D., McBryde, ES. (In review; pre-print at MedXriv 2022). Cost of tuberculosis-related aeromedical retrievals in the Torres Strait, Australia.	Conceptualisation, J.F. and D.J.; data collection and investigation, J.F.; writing – original draft preparation, J.F.; writing – review and editing, J.F., D.J., D.M., B.J.M., D.P. and E.S.M.; supervision, D.M., B.J.M. and E.S.M. All authors have read and agreed to the final version of the manuscript. This work was supported by the Torres and Cape Hospital and Health Service Revenue Manager located on Thursday Island; the Queensland Aeromedical Retrieval and Disaster Management Branch and the Queensland Ambulance Service provided access to data and revision of relevant sections within the manuscript. Proportion of the work that I undertook: 90%.
5.2	Foster, JB., Mendez, D., Marais, BJ., Denholm, JT., Peniyamina, D., McBryde, ES. (2022). Critical consideration of tuberculosis management of Papua New Guinea and cross-border health issues in the remote Torres Strait Islands, Australia. Tropical Medicine and Infectious Disease, 7 (9), 251.	Conceptualisation, J.F. and E.S.M., with J.T.D. in later stages; methodology, J.F. and E.S.M.; software, J.F.; formal analysis, J.F.; data collection and investigation, J.F.; writing – original draft preparation, J.F., writing – review and editing, J.F., D.M., B.J.M., J.T.D., D.P. and E.S.M.; supervision, E.S.M, D.M. and B.J.M. All authors have read and agreed to the published version of the manuscript. Proportion of the work that I undertook: 80%.

Chapter 6. Paediatric TB

Professor Ben Marais contributed to the study design, helped me explore analytic approaches and suggested using the new World Health Organization algorithm in the study. Professor Ben Marais and Professor Emma McBryde provided expert advice on chest x-ray interpretation. Dr

Steve Graham, as a subject matter expert in paediatric TB who led the development of the 2016 Union Desk Guide, was consulted and provided advice on undernutrition, malnutrition and severe acute malnutrition. Dr Steve Graham suggested the inclusion of Supplement 1 in the manuscript. Geraldine Sullivan created Figures 6.1.2 and 6.1.3 of the manuscript based on some design input from Professor Emma McBryde. Feedback from my supervisory team was requested, and edits and suggestions were implemented.

Contributions in Chapter 6

Chapter	Publication or Manuscript	Contribution of each author including the candidate
6	Foster, JB., Marais, BJ., Mendez, D., McBryde, ES. Critical review of tuberculosis diagnosis in children from Papua New Guinea presenting to health facilities in the Torres Strait Islands, Australia. Submitted to Global Health: Science and Practice, pending peer-review.	Conceptualisation and data collection, J.F.; methodology, J.F. and B.J.M.; review of five chest x-rays, B.J.M.; writing – original draft preparation, J.F.; writing – review and editing, J.F., B.J.M., D.M. and E.S.M.; supervision, E.S.M., D.M., B.J.M. All authors have read and agreed to the published version of the manuscript. Critical review of the manuscript, Professor Steve Graham and Dr Dunstan Peniyamina; review of five chest X-rays, Dr Chris Coulter; graphic design of Figures 6.1.2 and 6.1.3, Geraldine Sullivan. Proportion of the work that I undertook: 80%.

Chapter 7. Discussion and Conclusion

Feedback from my supervisory team was requested, and edits and suggestions were implemented.

Presentations / Conference Proceedings

Recipients of Presentations and Conference Proceedings

Recipients	Date
Torres and Cape Hospital and Health Service Board Members and Executive	29 April, 2021
Directors Quality and Safety, Queensland Department of Health	11 June 2021
National Tuberculosis Advisory Committee	22 June 2021
Menzies School of Population Health	7 October 2021
Selected to present at the Queensland Health Clinical Excellence Showcase	10 October 2021
National Tuberculosis Nurses' Clinical Meeting	7 July 2022
Medical Students, Global Health course, James Cook University	3 August 2022
Cross Border Health Issues Committee	31 August 2022

Doctoral Cohort Studies Program of Higher Degree Research Workshops and Mandatory Courses

Unit Code	Course Name	Date
16-RD7001-TSV-LTD-RT4	Planning the Research: Doctoral Candidates	29 February – 4 March 2016
16-RD7002-TSV-LTD-RT4	Situating the Research: Doctoral Candidates	11 July – 15 July 2017
19-RD7001-TSV-LTD-RT1	Planning the Research: Doctoral Candidates	29 January – 2 February 2018
19-RD7002-TSV-LTD-RT1	Situating the Research: Doctoral Candidates	29 January – 2 February 2018

Unit Code	Course Name	Date
RD7003	**Professional Development Program**	
	Candidacy details & using LearnJCU	29 February – 4 March 2016
	Working successfully with your advisory team	29 February – 4 March 2016
	Endnote	29 February – 4 March 2016
	Using databases for literature searching	29 February – 4 March 2016
	Writing a research proposal	29 February – 4 March 2016
	Critical review Journal Club	29 February – 4 March 2016
	Research Design Part 1	29 February – 4 March 2016
	Research Design Part 2	29 February – 4 March 2016
	Research Conduct Ethics	29 February – 4 March 2016
	Data Management	29 February – 4 March 2016
	Copyright and copywrongs	29 February – 4 March 2016
	Writing a literature review	29 February – 4 March 2016
	Academic Writing	29 February – 4 March 2016
	Goal setting and task engagement	29 February – 4 March 2016
	Time management	29 February – 4 March 2016
	Professional Writing and Editing	29 February – 4 March 2016
	Management of Data and Information in Research	29 February – 4 March 2016
	Plagiarism and iThenticate	29 February – 4 March 2016
	Copyright and Open Access	29 February – 4 March 2016
	Work Health and Safety Induction	29 February – 4 March 2016
	Research Integrity: The Responsible Conduct of Research	29 February – 4 March 2016
	Mixed Methods	11 July – 15 July 2017
	The nitty gritty of publishing: from manuscript preparation to publication	11 July – 15 July 2017
	Writing the significance section of grants & proposals	11 July – 15 July 2017

Unit Code	Course Name	Date
	Data Analysis – Quantitative SPSS	11 July – 15 July 2017
	Tips and Tricks in Word	11 July – 15 July 2017
	From Pre-completion to Thesis Submission	29 January – 2 February 2018
	Tying it all Together – The General Discussion	29 January – 2 February 2018
	Example Pre-completion seminar	29 January – 2 February 2018
	Research Communication	29 January – 2 February 2018
	Career Planning and Resources	29 January – 2 February 2018
	Journal Club	4 March – 8 March 2019
	Making a Pitch – Media Training	4 March – 8 March 2019
	Panel discussion – Life after the research degree	4 March – 8 March 2019
	Being a reviewer and responding to reviewers	4 March – 8 March 2019
	Research Commercialisation	4 March – 8 March 2019
	Data Analysis – Quantitative	4 March – 8 March 2019
	Abstract Writing	4 March – 8 March 2019
	Research translation and impact	3 February – 7 February 2020
	Journal Club	3 February – 7 February 2020
	Panel Discussion: Cohort Graduates	3 February – 7 February 2020
	Performing Research in the Hospital Environment	3 February – 7 February 2020
	Converting the thesis to pdf	3 February – 7 February 2020
	Respectful relationships	3 February – 7 February 2020
	Capacity building and mentoring	3 February – 7 February 2020
	Planning for Plan B	15 June – 19 June 2020
	Thesis Formats & Editing Rules	15 June – 19 June 2020

Unit Code	Course Name	Date
	Scaffolding Your Writing	15 June – 19 June 2020
	Creating Graphs and Tables	15 June – 19 June 2020
	Quantitative data analysis	1 February – 5 February 2021
	Values in collaborative research teams	1 February – 5 February 2021
	EndNote tips & troubleshooting	1 February – 5 February 2021
	Panel discussion: A tale of 3 graduates	1 February – 5 February 2021
	Working on wicked problems: A strengths-based approach to research engagement and impact	1 February – 5 February 2021
	Perfecting the Abstract	31 January – 4 February 2022
	Achieving your goals in uncertain times	31 January – 4 February 2022
	Small group discussion – Overcoming challenges in research	31 January – 4 February 2022
	Data analysis – Quantitative	31 January – 4 February 2022
	Presenting data – Quantitative	31 January – 4 February 2022
	Writing the final thesis discussion	31 January – 4 February 2022
	Getting Published - Predatory journals and conferences	31 January – 4 February 2022
	Editing for Concision	31 January – 4 February 2022

Abstract

Introduction: *Mycobacterium tuberculosis* is an airborne disease, and is the second leading cause of death due to an infectious agent after COVID-19.[2] While inroads have been made to reduce the burden of disease in developed countries due to improved living standards, public health legislation, state and national tuberculosis (TB) programs, Bacille Calmette-Guérin (BCG) vaccination and effective treatment,[3] TB continues to adversely affect Indigenous Australians in the Torres Strait Islands. The Torres Strait Islands sit adjacent to the Western Province of Papua New Guinea (PNG), where TB is endemic and where there is established and ongoing TB transmission across this international border.[4] To deliver the best possible healthcare in this region, frontline clinicians have a responsibility to understand and respond to epidemiological risk factors of TB disease. Epidemiological research allows for recognition of populations most at risk, and identification of population dynamics that are evidence-based and can enable programmatic changes that align with the ambitious targets of the World Health Organization's 'End TB' Strategy.

Methods: Residents of the Torres Strait Islands and PNG nationals that sought healthcare in the Torres Strait between 2000 and 2020 were included in the research. This included patients with presumptive TB or with a TB diagnosis. Statistical Analyses: For descriptive data, continuous variables were assessed for normality and either means and 95% confidence intervals or medians and interquartile ranges presented. For binary outcome data, Exact tests were used to analyse against categorical / binary predictor variables. Logistic regression was used when more than one predictor was being considered. For time to event data, appropriate analyses with log-rank tests were used to determine time to event characteristics and Cox proportional hazards test used to consider factor data. For other continuous outcome data, multivariate models and generalised linear models were constructed to assess factors for determining complex outcomes. Kappa tests were used to measure inter-rater reliability.

Results: In paper 1, we determined that 96% of all microbiologically confirmed pulmonary TB cases were diagnosed within the first two specimens collected, and that 93% of cases were diagnosed within the first two specimens collected in children aged <15 years. A smear positive result was 2.84 (CI 1.08, 7.46) times as likely in PNG nationals compared to residents of the Torres Strait Islands. In paper 2, we showed that among drug resistant TB, multidrug-resistant TB was identified as the dominant strain in the Torres Strait / PNG border region, with peaks

in case notifications occurring in 2007, 2010 and 2018. Isoniazid mono-resistant (INH-mono R)-TB reached peak dominance in the region in 2011, with no cases on INH-mono R-TB observed after 2014. Mabadauan, Ture Ture and Daru were identified as drug resistant (DR-TB) 'hot-spots' however, the distribution of cases into neighbouring communities was minimal. Females were 2.2 (*p* .04) times as likely to be diagnosed with MDR-TB. Ethionamide resistant (ETO-R)-TB was identified in MDR-TB patients and only nine MDR-TB cases were not resistant to ETO. Paper 3 described some of the challenges in managing MDR-TB cases across the international border. Paper 4 identified that the overall median time from onset of symptoms to effective treatment commencement between 2000 and 2020 for DR-TB patients was 124 days. The median time to treat significantly reduced since the establishment of the Torres and Cape TB Control Unit in 2016, compared to previous TB programs (2000-2005 p 0.04; 2006-2012 p <0.001). New cases were significantly associated with reduced treatment delay (new vs past treatment p 0.02). Paper 5 demonstrated that 29% of patients diagnosed with DR-TB between 2000 and 2020 had a poor outcome, and that immunocompromised patients had an increased frequency of poor outcome (p <0.05). Patients with a low lymphocyte count were significantly associated with having a poor outcome (p <0.05). The likelihood of patients having a good outcome statistically significantly increased by 50% with each incremental TB program year group. Being a close contact of a known TB case reduced the odds of a poor outcome occurring (*p* .008; OR .306). Paper 6 demonstrated that the total cost to medically evacuate and manage one exemplar PNG patient with pulmonary TB was $124,280 whereby 54% of that cost was attributed to travel. If all aeromedical evacuations cost a similar amount to our case study, then funding provided by the Australian Commonwealth Department of Health to care for PNG patients entering the Australian health system via the Torres Strait Protected Zone falls short by $7.5million per annum. Paper 7 identified an inconsistent application of aeromedical retrieval policy by Rural Generalist Practitioners in the Torres Strait. Scoring tools embedded in local policy do not identify the most serious of TB case presentations in border clinics. Human rights, ethical and moral issues were identified, leading to potential burden on frontline clinicians. Paper 8 identified that paediatric diagnostic scoring tools used in other settings are not appropriate for use in the Torres Strait / PNG border region and identified a need for the development of a TB diagnostic tool for the paediatric population.

Conclusion: With high numbers of patients presenting to Australian border clinics during the study period, this research provides an understanding of the epidemiological profile of TB in the Torres Strait / PNG region in patients with both presumptive and diagnosed TB. Potential

correlations based on the evaluation of patient outcomes in relation to diagnostics, distribution, delays, deterioration detection and frontline decision making have been identified, as has a shift in the epidemiological profile over time. This contribution to knowledge will allow the local health service and TB Unit to implement evidence-based policy changes and improvements to programmatic management of TB. Despite the concerted efforts of four different models of TB care in the region over 20 years, this research demonstrates that healthcare in the Torres Strait / PNG region is not always accessible, equitable, ethical or effective. It is of utmost importance that clinicians on the frontline are given the opportunity to reconcile these truths by reimagining health care systems that support patients on both sides of the international border.

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6. TCHHS. Appendix J3 *Initial Visit form (PNG nationals)*. In Appendix J2 Procedure: Management of Papua New Guinea Nationals accessing healthcare within the Australian Islands of the Torres Strait Protected Zone, presumed to have or diagnosed with tuberculosis. Cairns, Queensland: TCHHS.
7. TCHHS. Appendix J4 *TB Screening - PNG national escort algorithm*. In Appendix J2 Procedure: Management of Papua New Guinea Nationals accessing healthcare within the Australian Islands of the Torres Strait Protected Zone, presumed to have or diagnosed with tuberculosis (Appendix 3). Cairns, Queensland: TCHHS.
8. TCHHS. Appendix J5 *TB Screening – PNG national patients requiring Medivac algorithm.* In Appendix J2 Procedure: Management of Papua New Guinea Nationals accessing healthcare within the Australian Islands of the Torres Strait Protected Zone, presumed to have or diagnosed with tuberculosis (Appendix 2). Cairns, Queensland: TCHHS.

9. TCHHS. Appendix J6 *Policy: Papua New Guinea traditional inhabitants presenting to Queensland Health facilities within the Australian Islands of the Torres Strait Protected Zone* (TCHHS-CLIN-POL-0090). Cairns, Queensland: TCHHS.
10. TCHHS. Appendix J7 *Procedure: Papua New Guinea traditional inhabitants presenting to Queensland Health facilities within the Australian Islands of the Torres Strait Protected Zone* (TCHHS-CLIN-1,8-PRO-1244). Cairns, Queensland: TCHHS.
11. TCHHS. Appendix J8 *Clinical Management of Papua New Guinea traditional inhabitants presenting to TCHHS facilities flowchart.* In Appendix J7 Procedure: Papua New Guinea traditional inhabitants presenting to Queensland Health facilities within the Australian Islands of the Torres Strait Protected Zone (Appendix 1). Cairns, Queensland: TCHHS.
12. TCHHS. Appendix J9 *Management of patients with suspected pulmonary tuberculosis throughout the Torres and Cape Hospital and Health Service* (TCHHS-CLIN-1-PRO-0572). Cairns, Queensland: TCHHS.
13. TCHHS. Appendix J10 *Initial Visit and Contact Tracing form used in the Torres and Cape Hospital and Health Service for residents of the Torres Strait and Cape communities.* Cairns, Queensland: TCHHS.
14. TCHHS. Appendix J11 *Initial Visit and Contact Tracing form (Papua New Guinea nationals).* Cairns, Queensland: TCHHS.

Figure 0.1: The Wet Season Rolls in, Thursday Island (Foster, 2016).

Summary

The overall aim of this PhD was to conduct epidemiological research that would lead to improvements in local policy and practice for tuberculosis diagnosis and management. There is considerable scope to retrospectively use various data that can facilitate strategies to augment TB case detection and improve local processes. This is particularly important in the Torres Strait region due to its proximity to the tuberculosis-endemic Western Province of PNG which has potential to increase the risk of exposure. Evaluation of routine surveillance data, review of TB cases and epidemiological analysis of the host population is required to determine risk factors and chains of transmission links in the Australian / PNG cross border region. The End TB Strategy was used as a theoretical framework with which to select research problems and direct programmatic priorities. This research may aid in the estimation of cross border transmission risk as well as onward transmission of TB, which may in turn inform programmatic change.

Aims and Objectives

Aim 1. Investigate Cross-border TB Disease Epidemiology.

Review and synthesize current evidence and new data to explore historical and current TB management of residents of the Torres Strait Islands and PNG nationals accessing TCHHS facilities in the Torres Strait Protected Zone (TSPZ) to provide an understanding of disease epidemiology.

Objectives

- Explore the history of TB control in Indigenous populations in Northern Australia.
- Determine the known risk factors for transmission in Indigenous populations in the Torres Strait / PNG border region.
- Identify the gaps in the literature related to the management of TB in the Torres Strait / PNG border region.
- Ascertain the smear negative status among patients diagnosed with PTB in the Torres Strait Islands.

- Determine the geospatial distribution of DR-TB in the Torres Strait / PNG international border region.
- Explore the distribution of different types of DR-TB in the Torres Strait / PNG international border region.
- Identify predictors of mono, drug-resistant and multi-drug resistant TB in the Torres Strait/PNG international border region
- Ascertain the median time to effective treatment commencement, factoring in changes to programmatic management of TB over time.
- Find out the factors that contribute to a reduction in the times from onset of symptoms to effective treatment commencement.
- Determine predictors of unfavourable outcome for patients with DR-TB.

Aim 2. Identify opportunities for evidence-based enhanced policy and practice for the management of TB in the region (Translational Research).

Explore policy and practice of TB services, and how these shape TB management in the Torres Strait / PNG international border region. Provide locally-derived evidence to support new approaches to improve the management of all patients with presumptive TB and active TB disease in this region.

Objectives

- Explore the themes that underpin the global management of TB in challenging circumstances.
- Find out if the themes identified in the global management of TB in challenging circumstances apply to managing TB in the Torres Strait / PNG border region.
- Ascertain if two specimens sufficient for the diagnosis of pulmonary TB in the remote Torres Strait Islands.
- Research the quality, collection modality, and transportation of specimens and determine if these affect the diagnostic yield.
- Ascertain the constraints of managing shared MDR-TB patients across an international border.

- Explore the role of advanced diagnostic technology in reducing total time to effective treatment.
- Determine if the quality and collection modality of specimens affect the diagnostic yield in children.
- Identify if specific biomarkers are predictive of unfavourable outcome in DR-TB patients.

Aim 3. Identify opportunities for strengthened cross-border communication and collaboration between Australia and PNG health services to better manage TB in the region.

To identify opportunities to strengthen engagement between TB programmes in the Torres Strait Islands and Daru Island, PNG.

Objectives

- Identify opportunities for strengthening engagement between Australia and PNG health care and health promotion services.
- Ascertain if changes to the clinical management of DR-TB over time impacted on the outcomes of patients diagnosed with active TB disease.

Aim 4. Assess the aeromedical evacuation efficiency for TB in the Torres Strait and evaluate decision-making for PNG nationals with presumptive TB at the Australia / PNG border.

Investigate the efficiency and outcomes of aeromedical evacuation processes for TB management in the Torres Strait Islands and evaluate the decision-making consistency and equity for PNG nationals with presumptive TB presenting at the Australia / PNG international border.

Objectives

- Determine if funding provided by the Australian National Department of Health through National Partnership Agreements is sufficient to cover the cost of providing care to PNG nationals seeking healthcare via the TSPZ.
- Critically examine the level of adherence of clinicians working in the Torres Strait to local policy related to clinical deterioration and aeromedical evacuation criteria.
- Examine current scoring systems identify the most serious of presumptive TB case presentations at the international border.
- Determine if clinical deterioration detection scores used in the Torres Strait, sufficiently sensitive to detect deterioration in patients with presumptive TB.

Aim 5. Compare Torres Strait paediatric TB diagnostics with international methods to improve child TB detection.

Evaluate and compare the current paediatric TB diagnostic methods in the Torres Strait against internationally recognised approaches to enhance timely and effective TB diagnosis in children.

Objectives

- Outline the epidemiological profile of paediatric patients diagnosed in the Torres Strait / PNG border region.
- Determine if TB is under-diagnosed or over-diagnosed in the Torres Strait / PNG border region when current practice is benchmarked against diagnostic tools used in other comparable settings.
- Explore opportunities to enhance current diagnostic methods to incorporate additional measurement tools to identify patients at risk of poor outcome and increase likelihood of reduced time to treat.
- Examine current tools used for the diagnosis of paediatric TB and determine if these are sufficiently sensitive and specific for the diagnosis of paediatric TB in the region.
- Ascertain if there a TB scoring tool that can be modified for use in the Torres Strait, that has greater sensitivity and specificity than current diagnostic methods used for the paediatric population.

Development of Research Questions

After undertaking a thorough review of existing literature to identify research gaps, I ascertained the feasibility and significance of the research. A systematic process followed that integrated thematic analysis of the literature with known or anticipated programmatic gaps in clinical care. It is upon this foundation that most research questions within this thesis were constructed.

Development of research questions within this thesis was, in some instances, an iterative process. As data were collected, reviewed, and analysed, there were some occasions whereby preliminary results suggested there may be value in refining the study's inclusions or broadening the scope by adding supplementary questions. Further, as with any edifice, research builds on the foundation of existing knowledge. During this thesis, when a study uncovered new evidence, this at times provided a platform for subsequent questions to be asked.

Structure of the Thesis, Publications and Presentations

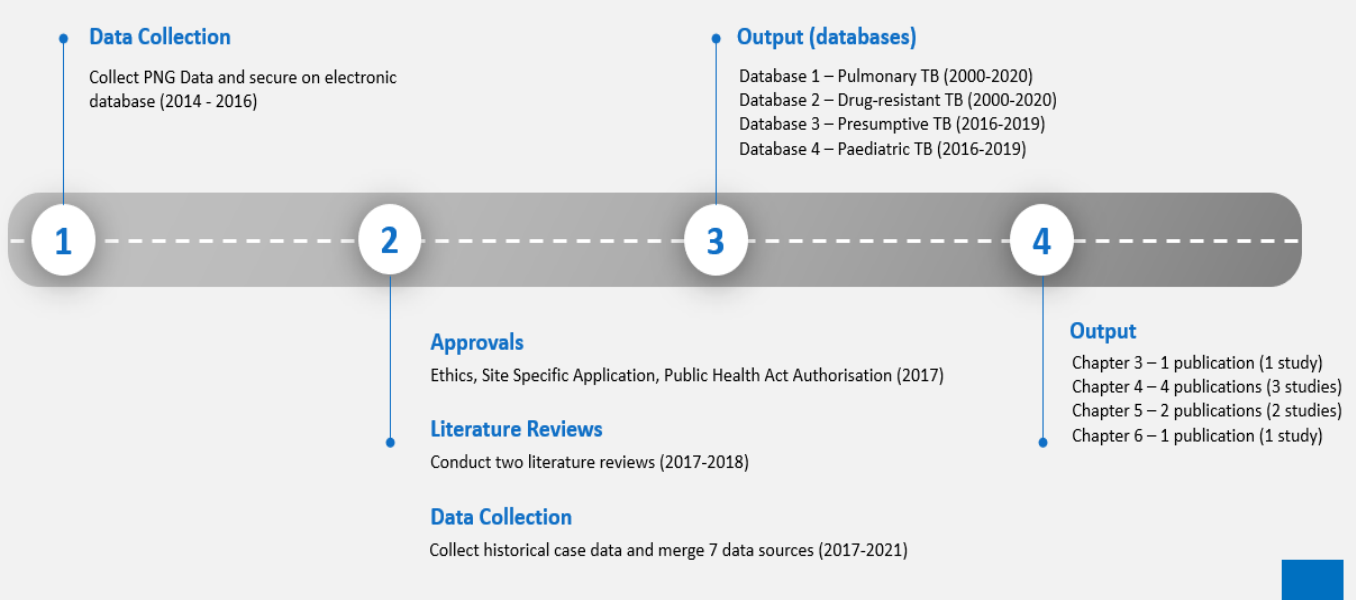

Figure 0.2: PhD Roadmap.

Chapter Overview

Chapter 1, Part A: Scoping Review – Managing Tuberculosis Under Challenging Circumstances (Lessons from International Settings)

This first chapter describes the global epidemiology of TB, pathophysiology of disease, diagnostics, disease sites, drug-resistance, treatment and transmission risk. This chapter also synthesizes available literature and identifies common themes when managing TB under challenging circumstances and during significant population events.

Chapter 1, Part B: Scoping Review – Managing Tuberculosis in Northern Australia, Torres Strait and Papua New Guinea (Previous Findings and Observations from the Region)

This chapter explores the history of TB management in Northern Australia, summarises challenges identified in Chapter 1, Part A, as they apply to the Torres Strait/Papua New Guinea border region, and describes programmatic management of TB in the Torres Strait.

Chapter 2: Data Collection

This chapter describes sources of data used within this thesis and the process of data collection.

Chapter 3: Diagnostic Yield

This chapter quantifies the diagnostic yield in patients diagnosed with microbiologically confirmed pulmonary TB disease. This chapter also provides epidemiological insight into smear status in patients with pulmonary TB and examines factors that can impact diagnostic yield.

Chapter 4: The Rise of Drug-Resistance

This chapter provides an overview of specific challenges in managing patients with multidrug-resistant TB across the Australia / PNG international border. Using case notification data over two decades, this chapter explores and quantifies differences over time in regards to patient outcomes and effective treatment commencement delays in drug-resistant TB cases. This chapter also provides spatiotemporal analyses of the rise of drug-resistance at the Australia /

PNG border with separate analyses demonstrating predictors of different types of mono and multidrug-resistance.

Chapter 5: High Price

This chapter examines Federal funding for TB management in the Torres Strait and provides a detailed cost analysis of an exemplar TB patient from PNG that required aeromedical evacuation to tertiary health facilities in Australia. Using locally derived data of presumptive TB case presentations, this chapter also critically examines response to patients with serious presentations or clinical deterioration and clinician adherence to local policy regarding evacuation. This chapter finds that adherence is inconsistent and the assessment tool itself misses serious cases important to the region – severe malnutrition. The chapter therefore proposes targeted diagnostic measurements of malnutrition to increase awareness of severely unwell children.

Chapter 6: Paediatric Tuberculosis

This chapter compares existing diagnostic tools – clinical scoring systems for tuberculosis - used in the paediatric population with two diagnostic tools used in other settings to determine if under or overdiagnoses are occurring in the cross border paediatric population.

Chapter 7: Discussion, Conclusion and Recommendations

This chapter presents the key findings from the research. It also includes a description of the translational impact that the findings of the thesis has had to date, had on the programmatic management of TB in the region. A list of programmatic improvements that were undertaken or planned to be undertaken as a direct result of this research have been included, with recommendations for further improvements and research in the area.

Linking the Publications

The seven studies and eight papers in this thesis are linked to each other. The paper in Chapter 4.2 contextualised the challenges associated with the management of TB at the Torres Strait / PNG border. The paper in Chapter 4.3 identified excessive delays in symptom onset to effective treatment and predictors of these delays in patients with DR-TB. The paper in Chapter 3 identified good diagnostic yield in children with PTB in the region, and confirmed that two sputum specimens are sufficient for the diagnosis of PTB, thus reducing diagnostic delay. The

paper in Chapter 4.4 identified predictors associated with unfavourable outcome in DR-TB patients. The paper in Chapter 4.1 shows spatiotemporal trends, illustrates DR-TB case notifications over time, and identifies factors associated with different types of drug resistance. The paper in Chapter 5.1 describes the costs associated with managing PNG nationals with presumptive TB at the border. The paper in Chapter 5.2 describes the operational activities and available tools that underpin decisions made by clinicians at the international border. The paper in Chapter 5.2 also examines the ability of available scoring tools used in the region to detect deteriorating TB patients. The paper in Chapter 6 then compares the utility of paediatric TB scoring tools used in other settings with known paediatric TB case diagnoses and modifies these tools to compare with paediatric diagnostics in the Australia / PNG setting.

Table of Contents

List of Figures

List of Tables

List of Acronyms and Terms

ACRONYM / TERM	EXPLANATION
AFB	Acid fast bacilli
ABF	Australian Border Force
ABS	Australian Bureau of Statistics
ACT	Australian Capital Territory
AIDS	Acquired Immune Deficiency Syndrome
AIHW	Australian Institute of Health and Wellness
ARDMB	Aeromedical Retrieval and Disaster Management Branch
ATAGI	Australian Technical Advisory Group on Immunisation
AUD	Australian Dollars
AUSLAB	Clinical and Scientific Information System using to store pathology results in Queensland Health
BCG	Bacille Calmette-Guérin
Best Practice	An electronic medical record used in the Torres and Cape Hospital and Health Service
CDC	Centers for Disease Control and Prevention
CHHHS	Cairns and Hinterland Hospital and Health Service
Clinical Collaborative Group	Originally commissioned by the Torres Strait Cross Border Health Issues Committee, this group comprised of representatives from Queensland Department of Health, Torres and Cape Hospital and Health Service, Cairns and Hinterland Hospital and Health Service and Daru General Hospital
Continuation phase	The final four to seven months of treatment for drug-susceptible TB is known as the continuation phase
Cross-border	The Australia/Papua New Guinea international border region
CXR	Chest x-ray
DFAT	Department of Foreign Affairs and Trade
DoH	Department of Health
DOT	Directly Observed Therapy (DOT) refers to a strategy where a healthcare worker or another trained individual directly observes a patient taking their medication. This method ensures that the patient consumes the correct dosage at the right time, enhancing the likelihood of treatment success and decreasing the chances of drug resistance.
DOTS	Directly Observed Therapy (Shortcourse) is the World Health Organization-recommended strategy for TB control and has been recognized as a highly efficient and cost-effective method. The term "short-course" refers to the relatively short duration of treatment for standard TB (typically 6 months), compared to older, less effective regimens that required a longer period of treatment.

DOTS-Plus	DOTS-Plus is an extension of the standard DOTS (Directly Observed Treatment, Short-course) strategy, specifically designed to manage multi-drug resistant tuberculosis (MDR-TB). While the basic DOTS approach is fundamental to tuberculosis control, DOTS-Plus focuses on the special needs and challenges posed by patients with MDR-TB.
DR-TB	Drug resistant tuberculosis
Effective treatment	Tuberculosis medication regimen
End TB Strategy	The World Health Organization's End TB Strategy is a framework that aims to assist countries detect, diagnose and treat tuberculosis and ultimately, end the TB epidemic
PACS	Enterprise PACS is a radiology informatics software used in Queensland Health facilities
EPTB	Extrapulmonary tuberculosis
ETO	Ethionamide
ETO-R	Ethionamide resistant
FNA	Fine needle aspirate
FNQ	Far North Queensland
FS-TB	Fully susceptible tuberculosis
HBCIS	Hospital Based Corporate Information System
HHS	Hospital and Health Service
HIC	Cross Border Health Issues Committee
HIV	human immunodeficiency virus
IGRA	interferon-gamma release assays
IHW	Indigenous Health Worker
INH; H	Isoniazid
INH-R	Isoniazid-resistant
Intensive phase	The first two months of treatment for drug-susceptible TB is known as the intensive phase
JCU	James Cook University
LTBI	Latent TB Infection
LTFU	Loss to follow up
MDR-TB	Multidrug-resistant TB
MUAC	Middle upper arm circumference
MTB	*Mycobacterium tuberculosis*
NPA	National Partnership Agreement
NoCS	Notifiable Conditions System is used to record all notifiable conditions in Queensland
PHC	Primary Health Centre
PNG	Papua New Guinea
PNG national	In this thesis, refers only to a resident of Papua New Guinea that presents to a health facility in the Torres Strait Protected Zone
PPD	Purified protein derivative
Presumptive TB case	A person who presents to a health facility with signs and symptoms of tuberculosis
PTB	Pulmonary TB
PWH	Person with HIV

QLD	Queensland
Queensland Health	A State Government Department responsible for the public healthcare system in Queensland, Australia
RFDS	Royal Flying Doctor Service
RR-TB; RR	Rifampicin resistant TB
RRRC	Reef and Rainforest Research Centre
Smear or AFB positive TB	Tuberculosis of the lungs in which acid-fast bacilli has been detected - these cases are typically more infectious than smear negative patients
Smear or AFB negative TB	Tuberculosis of the lungs in which acid-fast bacilli has not been detected - these cases are typically less infectious than smear positive patients
SMO	Senior Medical Officer
SS	Sputum specimen
TB	Tuberculosis
TB case	Tuberculosis that has been diagnosed clinically or via laboratory confirmation
TBCU	Tuberculosis Control Unit
TCHHS	Torres and Cape Hospital and Health Service
TI	Thursday Island
TIH	Thursday Island Hospital
The Viewer	The Viewer is a central source of electronic medical records across Queensland Health, including but not limited to x-ray, pathology, inpatient and discharge data
TSI	Torres Strait Islands
TSIRC	Torres Strait Island Regional Council
TSPZ	Torres Strait Protected Zone
URN	Unique record number
WHO	World Health Organization
Xpert MTB/RIF; Xpert	A rapid diagnostic tool that can detect TB and rifampicin resistance in under two hours
ZN staining	Ziehl-Neelsen (ZN) staining is a method for detecting acid-fast bacilli (AFB)

Figure 1.1 A Doctor Screens a Newly Arrived Tibetan Refugee for Tuberculosis in Dehradun, India (Foster, 2012)[1]

Chapter 1: Contextualising Tuberculosis
Part 1: Tuberculosis and Global Challenges

1.1 Managing Tuberculosis Under Challenging Circumstances: A Scoping Review—Lessons from International Settings

Aims:

1. Identify characteristics of challenging settings that required intensified, strategic, unique, or complex efforts in the field of tuberculosis management.
2. Contrast and compare TB management practices in complex settings.
3. Identify common themes across the relevant literature.

At the time I was developing the research question for this chapter, I was also establishing the Torres and Cape Tuberculosis (TB) Control Unit. While TB-related operational policies and procedures had previously been available to TB Control Units in Queensland, the responsibility had shifted to Hospital and Health Services to develop, maintain, and govern these policies and procedures. The Torres and Cape TB Control Unit is the only program in Australia that operates at an international border. From a TB management perspective, there were stark disparities between what was available for residents of the Torres Strait Islands and the neighbouring Treaty villages of Papua New Guinea in terms of basic standards of living conditions, human resources required for healthcare and access to diagnostics and treatment.

Although past versions of TB-related operational policies and procedures could still be sourced for use within this context, these policies and procedures were not written with a remote Indigenous community with unusually high incidence rates of TB in mind. They were not written to support a TB Control Unit that provided TB care less than 5 kilometres from Papua New Guinea, a country with one of the highest rates of multidrug-resistant TB in the world. In the Torres Strait, the heightened risk of TB exposure, transmission, and infection as well as remoteness add to the complexity of managing TB in a cross-border region. Hence, ensuring a strong foundation for evidence-based policy formulation to support the management of TB in the Torres Strait / PNG border region required a review of how TB is managed in other challenging settings.

1.2 Contribution

My contribution to this chapter was as follows:

- I ran all database searches in PubMed, Medline, and Scopus, and accessed sources of grey literature to seek for information and research on managing TB in challenging circumstances.
- I re-ran the database searches following the same search strategy as I was preparing my thesis for submission. Some additional records identified through other sources were cited in this scoping review and in the thesis studies.
- I attended workshops about writing literature reviews via the Cohort Doctoral Studies Program at James Cook University.
- I was the lead author of this chapter and shared drafts with my supervisory team.
- I took one photograph used in this chapter and have acknowledged the photograph that I did not take, and I sought appropriate permissions to use some figures in this chapter.
- I identified themes within the literature, which were then utilised in Chapter 1b – Managing tuberculosis in Northern Australia, the Torres Strait and Papua New Guinea (previous findings and observations from the region).
- I developed a data chart to summarise the characteristics of the literature sourced for this scoping review.

1.3 Background

> Globally, TB control is challenged by antiquated and inadequate tools; diagnostic tests that are 125 years old; an 85-year-old vaccine; and drugs that, fundamentally, have not changed for 50 years.
>
> - Dr P. Small, Deputy Director Tuberculosis Delivery Program, Bill and Melinda Gates Foundation; personal communication, September 2012

Tuberculosis (TB) is a respiratory infection caused by the bacteria *Mycobacterium tuberculosis*, typically affecting the pulmonary system, and causing chronic cough, night sweats, and weight loss.[2] TB is treatable and curable; however, if left untreated, TB leads to death in approximately half of the individuals with active disease and remains a major cause of death worldwide.[3] While first-line antibiotic treatment consisting of four main drugs (isoniazid, rifampicin, ethambutol, pyrazinamide) ingested daily for at least 6 months is

consistently used to treat drug-susceptible TB (DS-TB), 4-month regimens (isoniazid, rifapentine, moxifloxacin, pyrazinamide) recommended by the World Health Organization (WHO) have not yet been widely incorporated.[4] New drugs such as bedaquiline and delamanid used to treat rifampicin-resistant and multidrug-resistant TB (MDR-TB) – TB that is resistant to both isoniazid and rifampicin - have been gradually introduced to second-line drug regimens over the past five years.[5] Adherence to the full course of TB treatment can be difficult for many people, owing largely to side effects of TB drugs and the requirement to commit to a lengthy antibiotic treatment course.[3] Prior to the introduction of new TB drugs into the global drug market, treatment of MDR-TB used to take up to 24 months to successfully treat, whereas with the introduction of new second-line drugs, it is hoped that shortened regimens will improve adherence issues and loss to follow up.[5]

Global TB data that includes the years leading up to and during the COVID-19 pandemic are concerning and it is evident that TB control efforts have been overshadowed by the COVID-19 pandemic. The. In 2018, prior to the COVID-19 pandemic, there were an estimated 10 million cases of active TB disease globally, in which 1.5 million died.[6] In 2018, 3.5% of newly diagnosed patients and 18% of previously treated patients had MDR-TB.[7] In 2019, 7.1 million cases were reported and this decreased further to 5.8 million during the pre-vaccination height of the COVID-19 pandemic in 2020, suggesting that there were many millions of missing, undiagnosed or unreported cases.[8] Progress to find and treat TB cases has been adversely affected by pandemic-related lockdowns and reduced access to healthcare services.[9] Further, the WHO has reported that one in three people that needed to commence on effective treatment for drug-resistant TB (DR-TB) in 2020 did not receive it.[2] This will almost certainly impact the ambitious targets of the 'End TB Strategy'.

The 'End TB Strategy' proposed by the WHO aims to reduce the incidence of TB by 90% before 2035 and addresses the ongoing need to manage TB.[10] This strategy requires effective TB prevention, integration of patient-centred care, incorporation of prompt diagnosis and screening among those with known risk factors such as human immunodeficiency virus (HIV).[10] Policy and system supports, including the commitment of governments; and appropriate national strategies are necessary to meet the needs of the most vulnerable and at-risk communities.[10]

Achieving the ambitious goals of the 'End TB Strategy' is especially challenging in circumstances where vulnerability is high and patients are less likely to have access to required

diagnostics, treatment, and follow-up care. Despite a high number of cases and high mortality rates worldwide, *Mycobacterium tuberculosis* infection – also known as Latent TB Infection (LTBI) – progresses to disease in only 5–10% of immunocompetent individuals,[11] with the greatest risk during the first 2–5 years following infection. In children, vulnerability is highly age dependent; younger children are more vulnerable,[12] with up to 50% of infected infants (aged <1 year) progressing to TB disease[13] and nearly all disease progression occurring during the first year after primary infection.[14] Reactivation is also more frequently observed in people with HIV (PWH) and in malnourished children of smear-positive parents, immunologic tests for TB infection such as the tuberculin skin test (TST) are commonly negative[11] and the chest x-ray (CXR) can often look normal.[15] While the risk of missing TB disease is the main concern, the risk of missing TB infection is also problematic.

1.3.1 Diagnosis and Treatment (Chemoprophylaxis) of Latent TB Infection

Many countries with high burden of TB are categorised as low-and-middle-income countries.[16] In these countries, diagnostic tests to confirm mycobacterial infection, such as TST or interferon-gamma release assays (IGRA), may not always be available owing to logistical challenges or high costs, or considered to be less informative in settings with high levels of ongoing TB exposure.[17] LTBI cases are the seedbeds for future active cases, but without diagnostic tests to detect LTBI or provide chemoprophylaxis to treat the source infection, TB control programs may struggle to contain reactivation within vulnerable populations. The risk of missing TB infection can be mitigated by starting preventive therapy (also known as chemoprophylaxis) for all asymptomatic children with known TB exposure, irrespective of TST/IGRA results.[18]

Although chemoprophylaxis is available which can help prevent progression from TB infection to disease, clinicians must first ensure that the patient is free of active TB, as prophylactic drugs used to treat LTBI are also used to treat active TB disease.[11] This clinical step is crucial because incorrect administration of chemoprophylaxis to a patient with active TB may increase the risk of developing drug resistance and jeopardise the effectiveness of future TB treatment for this patient and for other patients.[15] However, if the End TB targets are to be achieved, increased chemoprophylaxis uptake may be required in high-burden settings to reduce the incidence of reactivated smear positive pulmonary TB.[17] For chemoprophylaxis to remain effective in high-burden areas, lifetime treatment – which may pose toxicity risks – may be required[11] however, more recent research suggests that liver injury may be reduced using a shorter set duration with

regular monitoring[19,20] or swapping out isoniazid for rifampicin. However, any decisions to initiate chemoprophylaxis must also take into consideration the risk of drug resistance, as it is possible that the bacteria will be resistant to the antibiotic chosen.[21]

Early diagnosis and effective treatment are the cornerstones of an effective TB control program, which coupled with targeted surveillance and monitoring of persons most at risk require substantial resources. Adding to the complexity are key socio-economic drivers of vulnerability such as alcohol misuse, overcrowding, malnutrition, and smoking, and these risk factors are associated with progression to active TB disease.[22] Globally, TB control programs aim to reduce transmission, prevent TB and development of resistance, reduce mortality and morbidity associated with TB, and maintain adequate surveillance systems.[2] The purpose of diagnosis and treatment of TB – especially infectious pulmonary forms – is to reduce transmission.[23] In much of the developed world including Australia, passive case finding, as a WHO Stop TB Strategy recommendation, is still implemented, whereby the premise of diagnosis largely relies on individuals presenting to health facilities with signs and symptoms of disease.[24] Once a case is diagnosed, infection control strategies are implemented to contain the public health risk, and treatment is commenced as soon as possible.[2] TB control programs facilitate treatment using chemoprophylaxis or monitoring with CXR surveillance for individuals who test positive for infection and are at risk of reactivating TB.[25] Such intensive human and financial resources are not typically available in developing countries with the highest burden.[25]

1.3.2 Diagnosis and Treatment of Active TB Disease

Diagnostic methods for active TB disease differ across low- and high-burden countries and are often symptom driven. In low-resource settings, acid-fast bacilli (AFB) microscopy may be the only diagnostic tool used, followed by Xpert® MTB/RIF assay or Molbio Truenat where available. Xpert is a nucleic acid amplification test (NAAT) that can detect TB and rifampicin resistance in under two hours.[26] Molbio Truenat is a battery-operated device that can produce initial results in less than an hour[27] but is not as widely used as Xpert. In high-resource settings, AFB microscopy is followed by Xpert, culture, and drug susceptibility testing. Pulmonary TB can start with an initial dry cough which progresses to a cough with sputum production and, occasionally, haemoptysis, although TB can manifest in heterogenous ways.[28] Although commonly listed as symptoms, fever and fatigue are unreliable features of the disease, as they are not always present. In cases of presumed pulmonary TB, sputum is collected using non-

invasive (voluntary expectoration) or invasive (bronchoscopy, induction, aspiration) methods depending on age and capacity.[15] Diagnostic confirmation is obtained via molecular methods such as NAATs and mycobacterial culture and often only available in the developed world with regulated laboratory support.[28]

Patients with complaints of localised chest pain or pleurisy are generally observed to have pleural TB disease which is considered extrapulmonary disease and often do not have any other signs and symptoms.[28] If pleural fluid can be tapped, both histological and microbiological evidence can be collected and analysed. Otherwise, pleural TB is a clinical diagnosis based on CXR findings. Other extrapulmonary disease diagnoses rely on site specific diagnostics. Where available, fine needle aspiration biopsy is used to identify TB lymphadenitis, whereas imaging modalities such as magnetic resonance imaging (MRI) or computerised tomography (CT) are useful in the diagnosis of TB of the genitourinary tract, bone and joints, central nervous system, and abdomen as well as in cases with disseminated disease.[28] Alternate non-site specific tests being developed to detect early TB, particularly in PWH, include lateral flow urine lipoarabinomannan (Urinary LAM) antigen detection, whereas second and next generation LAM assays such as FujiLAM, have greater sensitivity and may be of benefit in non-HIV populations.[29] Diagnosing both pulmonary and extrapulmonary TB is expensive, and modern diagnostic methods are often unavailable to meet clinical needs in developing countries.

Although TB is one of the oldest known infectious diseases in the world, the emergence of resistant strains of TB has been slow.[30] Prior to the introduction of anti-TB drugs in the mid-1900s, death was the most common outcome following a TB diagnosis.[30] The treatment for TB is a double-edged sword because the drugs used to achieve bacterial clearance are the same drugs leading to resistance. Streptomycin was the first anti-TB drug available in 1944; however, by 1946, over 85% of patients were resistant to it.[30] Similarly, p-aminosalicylic acid (PAS) was introduced in 1946,[31] with PAS resistance first reported in 1949.[30] However, when both drugs were used together to treat patients with TB, the pace of resistance development slowed.[30] Anti-TB treatment options were expanded in 1952 with the addition of isoniazid and again in 1961 with the addition of ethambutol, which replaced PAS.[31] In 1972, streptomycin was relegated as a second-line drug to treat drug-resistant TB and replaced by rifampicin and pyrazinamide to treat drug-susceptible TB. Thereafter, the WHO-recommended first-line TB drug regimens for drug-susceptible TB be comprised of isoniazid, rifampicin, ethambutol, and pyrazinamide for 2 months, followed by isoniazid and rifampicin for a further 4 months.[30]

However, these recommendations do not constitute a globally agreed treatment protocol and medication regimens differ across countries, within countries, and between physicians.[32]

Regimens used to treat DS-TB such as the one described above is ineffective in patients with DR-TB, as the drugs that patients are resistant to should not be used to treat disease in most cases.[33] It is agreed at a global level that various factors contribute to TB treatment success. These factors may include an adequate drug supply, monitoring drug therapy adherence through directly observed treatment short-course (DOTS), and support by health professionals. Some studies have shown that community-based support by the treating team was a more important predictor of treatment success than the regimen selected by the treating physician.[32]

The DOTS Strategy, where TB patients are observed ingesting each dose of treatment,[23] is dependent upon political commitment, sufficient human resources in the health sector, stable supply of medication, and the ability to monitor patients undergoing treatment effectively.[34] There are several considerations and limitations regarding the traditional approach to DOTS. The challenges associated with DOTS include its potential in exacerbating stigma and acting as a barrier to treatment access, particularly when DOTS is facility-based instead of being community or household-oriented.[35] Further, systematic reviews have yielded inconclusive evidence about the efficacy of DOTS in terms of treatment outcomes. It is worth noting that alternative methods such as electronic pill boxes, video-DOT, and 99DOTS have emerged to enhance patient-centric treatment, adherence, and support.[36,37]

Patients receiving treatment for infectious pulmonary TB are monitored carefully for evidence of smear conversion. Positive-to-negative smear conversion is required to ascertain an adequate response to treatment for pulmonary TB has been achieved.[23] When achieved, smear conversion not only represents a non-infectious status but demonstrates clinical improvement and efficacy of the chosen drug regimen.[38] Although most patients receiving effective treatment for drug-susceptible pulmonary TB are non-infectious long before smear or culture conversion is achieved (within days), many remain in isolation until bacteriological conversion is confirmed.[39] For patients with drug-resistant TB, the issue is not as straightforward, and there are no standardised de-isolation guidelines specific to this patient group.[39] This is particularly problematic in resource-poor regions with limited hospital beds, as it can take weeks or months for bacteriological confirmation of a non-infectious status.[39]

Failure to diagnose pulmonary TB cases as early as possible leads to transmission within communities. This is often the case in developing countries but is also evident during times of crisis, for example, in conflict settings or following natural disasters when health services are interrupted.[40,41] From both individual and public health perspectives, marked disruptions in social order or a breakdown of security and infrastructure can have devastating effects both on patients known to have TB and individuals with undiagnosed TB. When treatment is interrupted or not commenced, transmission risk is increased, as conflict or crisis often forces people into crowded and poor living conditions, which form an optimum breeding ground for this airborne disease among the most vulnerable individuals. Vulnerable sub-populations are often observed among the displaced, nomadic, mobile, remote, and Indigenous populations and frequently exhibit an increased risk of disease transmission.[40] In addition, TB transmission risk may increase in conflict or post-conflict areas owing to political instability, damaged health infrastructure, supply and security issues, lack of adequately trained staff, and an uncertain allocation of financial resources.[42] Complex emergencies due to natural disasters or presence of coexisting diseases may also hamper TB control efforts, especially when resources are already stretched and attention is focused on short-term goals rather than communicable diseases such as TB.[41]

Given that TB is both one of the oldest infectious diseases known to humankind and the leading cause of death from an infectious agent[8], it is evident that it is a challenging disease to control. Much of the burden of TB disease befalls people who live in low-and-middle income countries, and managing this disease requires innovative strategies, ideas, interventions. Although Australia is a high-income country, most TB diagnoses made in the Torres Strait, are in residents of a low and middle-income country - Papua New Guinea (PNG).[43] Globally, there are few locations where a high-income country borders a low-income country, and even fewer where TB is endemic at that border. In pursuit of the development of strong foundations for the local TB Control Unit in the Torres Strait, this scoping review was undertaken to explore a range of scenarios for managing TB in other challenging circumstances. Reviewing the literature and TB control strategies used during natural disasters, during times of conflict or post-conflict and at other international borders was with the aim of determining common themes in the literature from which strategies to prevent and control TB could be applied locally.

1.4 Methods

A structured scoping review was undertaken to describe the range of literature available relating to the management of TB under challenging circumstances, to identify common themes and gaps in the literature. Unlike systematic reviews, which focus on a particular set of questions or interventions with precise outcomes, scoping reviews can be used to map and clarify key concepts.[44] Scoping reviews are particularly relevant when a broad examination of key concepts is required to showcase evidence across various contexts (geographical, political, sociocultural, healthcare setting) and identify gaps in the field, at the practical frontline of healthcare delivery.[45]. It is important to note that as this is a scoping review, the output may not be comprehensive/exhaustive.

Although the term 'challenging circumstances' is ambiguous, it can be exemplified in environmental, physical, individual, financial, laboratory, and programmatic perspectives. A scoping review allows for breadth of coverage (rather than depth) as well as redefinition of parameters as familiarity with the literature increases.[44] It should be noted that scoping reviews do not involve a quality assessment of available literature but do provide a mechanism with which to summarise the literature and draw conclusions, particularly in areas where minimal research has been conducted.[44] The present scoping review was conducted using the Arksey and O'Malley[44] five-stage methodological framework, which aims to identify gaps in existing research literature.

Much of the published TB-related literature available to date includes words such as 'defaulter' and 'suspect'. A shift from judgmental or blame-placing language to patient-centred terminology is recommended by the World Health Organization and this change is being driven by the Stop TB Partnership.[46] In keeping with current recommendations, 'presumed' instead of 'suspect'; 'lost to follow-up' instead of 'defaulter', and 'unfavourable outcome' instead of 'poor outcome' has been used in this scoping review. It is important to note that the definition of treatment 'default' has changed over time. In the 1980's 'defaulter' meant that patients had missed three consecutive days of TB treatment in the intensive phase and >1 week in the continuation phase.[47] Today, 'defaulter' refers to a patient who has missed TB treatment for ≥2 consecutive months.[46]

1.4.1 Stage 1 – Identifying the research question

Purpose of the review: To describe the range of research on managing TB under challenging circumstances, to identify themes and identify gaps in the literature.

1.4.1.1 Research Question:

What are the common themes when managing TB under challenging circumstances?

1.4.2 Stage 2 – Identifying relevant studies

Key databases used to identify relevant literature included PubMed, Medline, and Scopus. Primary research studies, reports, and systematic reviews were included in the search strategy. After familiarisation with the literature, search terms that could be applied across all searches were developed post hoc. Between October and early November 2017, a literature search was performed using search terms including [‘conflict’ OR ‘natural disaster’ OR ‘refugee’] AND [‘tuberculosis’ OR ‘tuberculosis control’].

In PubMed, the search for ‘tuberculosis’ AND ‘natural disaster’ and ‘tuberculosis control’ AND ‘natural disaster’ yielded only 10 results. Search terms were then modified to include ‘earthquake’, ‘flood’, ‘cyclone’, ‘hurricane’, and ‘tsunami’; in combination with ‘tuberculosis’ and ‘tuberculosis control’, these terms yielded 130 results, including the original 10.

EndNote software was used to manage searches and records and remove duplicates. In mid-November 2017, database searches were repeated to include the additional search terms [‘post-war’ OR ‘remote’ OR ‘nomadic’]. Article reference lists were also used to source additional articles. Additional literature was manually added to EndNote, and duplicates were removed. All references were combined and saved in one folder in EndNote.

Grey (unpublished or non-commercial) literature was sourced from conference proceedings, government documents including fact sheets, parliamentary enquiries, reports and policy statements, theses, maps, and surveys. Grey literature was sourced using defined search terms in three ways: a) from university repositories to obtain academic grey literature including theses; b) from Google, limiting the search to the first 20 pages per search term; and c) from open-source repositories such as Trove and OpenGrey.

No publication date constraints were placed on literature searches, as it was important to incorporate a large variety of political and environmental landscapes and represent programmatic changes with the global rise, risk, and progression of MDR-TB. Foreign-language material was excluded owing to costs associated with translation. It is possible that, owing to this imposed restriction, relevant foreign-language publications were excluded.

The same search strategy was re-run to identify new literature published between December 2017 and December 2022, which did not alter the initial findings (see Figures 1.1.1 and 1.1.2 for the PRISMA and Appendix H2 for the associated Data Charts).

1.4.3 Stage 3 – Study selection

Inclusion and exclusion criteria were established to ensure consistency in decision making,[44] and literature was included or excluded based on the title or the abstract if the title was unclear. All references including those drawn from database searches and from articles cited in the reference list of other articles were reviewed. The full abstract of each included reference was then screened for relevance. If the relevance was unclear, the article was excluded. If the reference fit with the research question, it was included. Full text was then obtained for all included references.

Exclusion criteria: Foreign-language publications; oral histories; personal accounts; individual patient data meta-analyses; articles not relevant to research question; newspaper articles; notifiable disease reports; articles with a laboratory focus only; studies on Mycobacterium species other than *Mycobacterium tuberculosis* (e.g. non-tuberculous *Mycobacterium*, leprosy), vaccine and drug development, and TB in animals; book reviews; and immigration screening data in developed countries.

Inclusion criteria: Programmatic management of *Mycobacterium tuberculosis* under challenging circumstances and during significant population events such as natural disasters, civil unrest, or other mass crises.

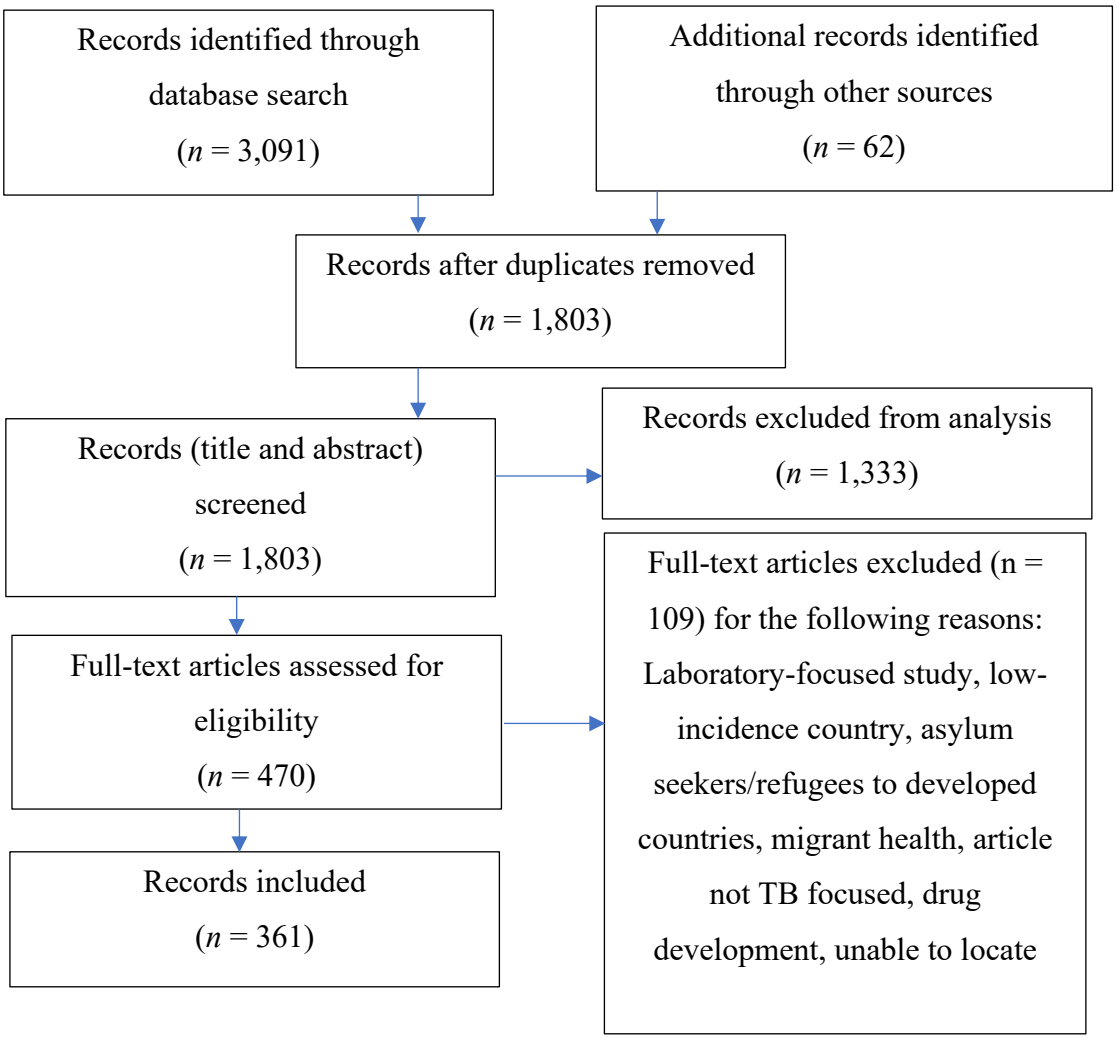

Figure 1.1.1 PRISMA Flow Diagram Detailing the Paper Selection Process for Research Question (What are the Common Themes When Managing Tuberculosis Under Challenging Circumstances?). PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[42]

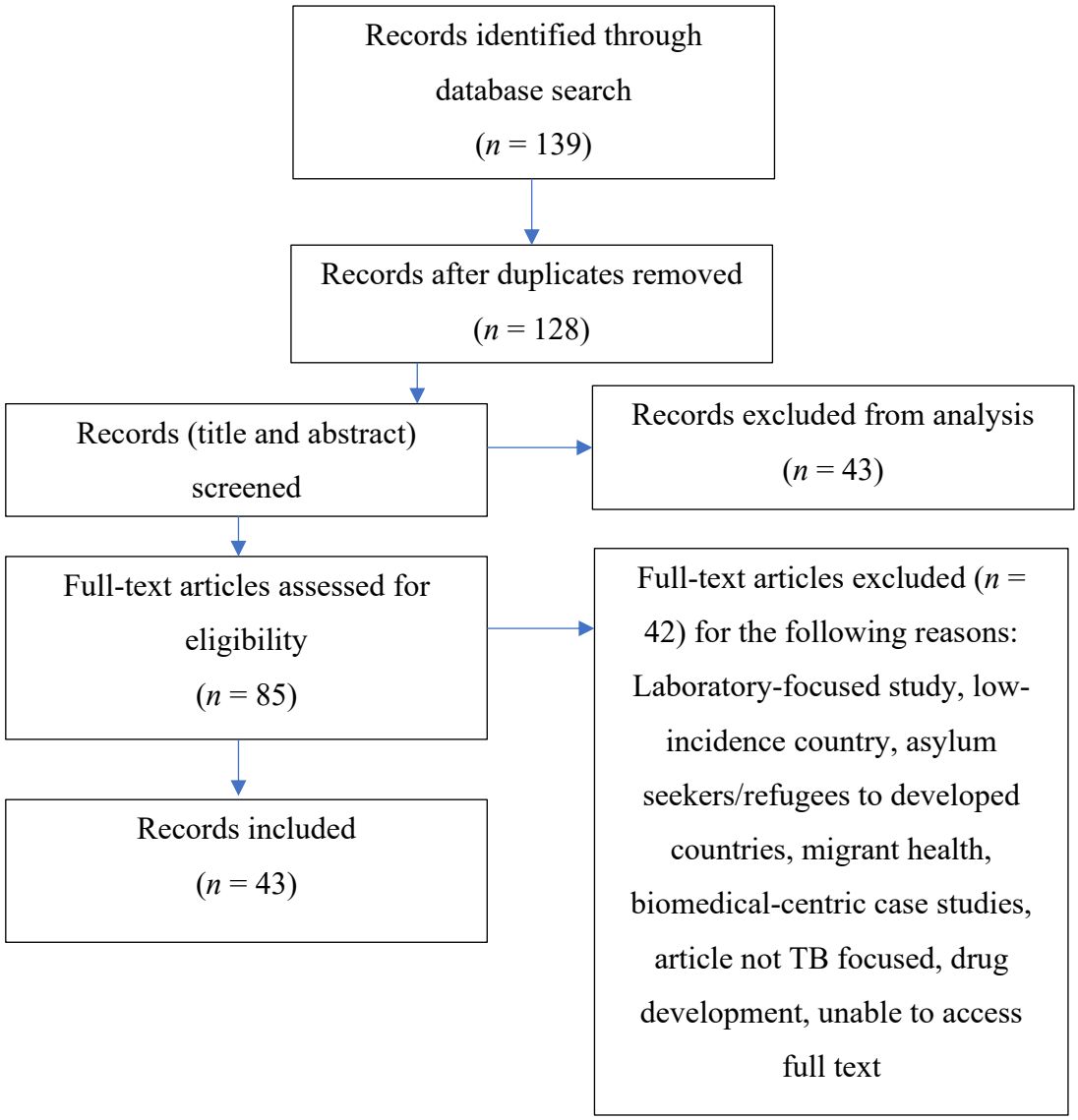

Figure 1.1.2 PRISMA Flow Diagram (December 2017 – December 2022) Detailing the Paper Selection Process for Question 1 (What are the Common Themes When Managing Tuberculosis Under Challenging Circumstances?)[48]

1.4.4 Stage 4 – Charting the data

A 'descriptive-analytical' framework was used to collect standardised information from each included publication. Author, year of publication, study location, type of article, intervention type and comparator (if any), study population (care recipient group post-conflict, natural disaster etc.), Study aims, methodology, outcome measures, and important findings were reviewed for each article. Excel was used to chart the data and record risk-based themes and programmatic themes for each selected reference (Appendices H1 and H2).

It should be noted that not all references contained all information required for a complete data review. Characteristics and breadth of geographic distribution of the literature were identified, and the references were then sorted into common themes.

1.4.5 Stage 5 – Collating, summarising, and reporting the findings

Simple numerical analysis was undertaken to produce tables and figures illustrating geographical location, type of article, and themes identified within the literature. The literature was also organised thematically to illustrate dominant areas of research in two ways. The first thematic analysis was undertaken to map the extent, nature, and distribution of risks associated with the management of TB in various challenging circumstances. The second thematic analysis was performed to review programmatic themes rather than risk-based themes. The primary unit of analysis was organised around programmatic themes that sat within commonly identified risk variables. Using a descriptive thematic narrative, findings are presented in this scoping review as major themes in the literature on managing TB in challenging circumstances (see **"Results"** section).

1.5 Results

A total of 361 documents were included in the initial scoping review and a further 43 documents were subsequently added in 2022. In total, 404 documents were included in the scoping review, with 322 that were peer-reviewed articles and 39 grey literature documents. Recipients of care were identified in the literature in six different study populations in challenging settings (natural disaster, post-conflict, conflict/fragile state, nomadic, remote/isolated, and cross-border settings). The breadth of geographic distribution of the literature is presented in Figure 1.1.3.

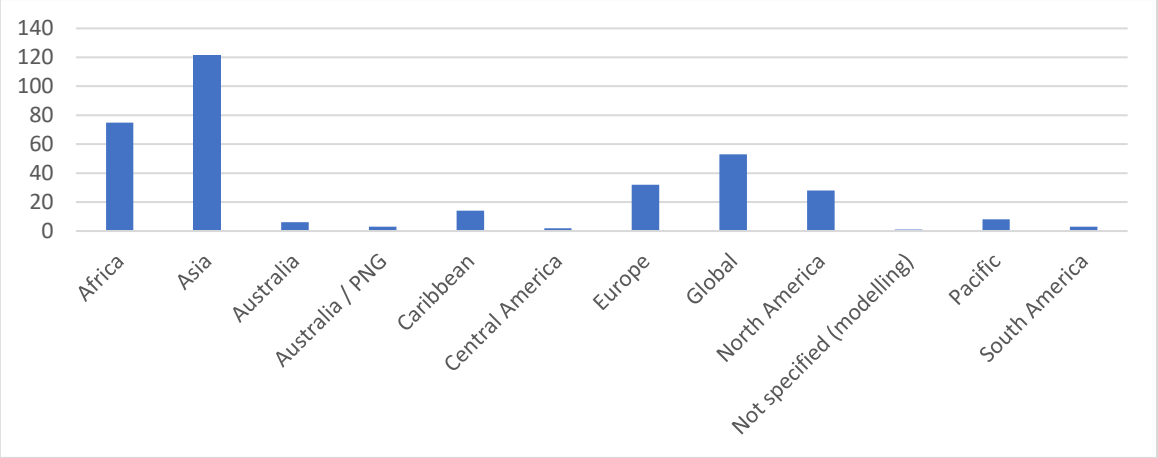

Figure 1.1.3 Geographical Distribution of Literature Identified to Address the Research Question 'What are the Common Themes When Managing Tuberculosis Under Challenging Circumstances?'

Although there were over 20 risk factors (conditions resulting in a high risk of disease transmission/conditions leading to programmatic challenges) identified, many overlapped within the references. Some were presented as perceived or known risk factors with a cursory mention, whereas others provided a more in-depth exploration of these variables. Overall, 16 main themes (Table 1.1.1) were selected according to breadth of coverage in the included literature.

The present scoping review focused on the following research question: What are the common themes when managing tuberculosis under challenging circumstances?

Table 1.1.1 Key themes identified in included studies regarding managing tuberculosis under challenging circumstances

Individual Risk Themes	Percentage/Number	Programmatic Challenge Themes	Percentage/Number
Overcrowding	31 (*n* = 113)	Climatic challenges	16 (*n* = 58)
Poor nutrition	37 (*n* = 133)	Geographic challenges	13 (*n* = 46)
Personal financial constraints	32 (*n* = 115)	Damaged health infrastructure	15 (*n* = 55)
Health illiteracy	14 (*n* = 49)	Limited human resources	27 (*n* = 99)
Treatment delay	30 (*n* = 107)	Insecurity	24 (*n* = 86)
Comorbidities	33 (*n* = 119)	Treatment interruptions	41 (*n* = 149)
		Disrupted health services	23 (*n* = 82)
		Access issues	40 (*n* = 145)
		Allocation of financial resources	36 (*n* = 129)
		Cross-border management/control of TB	23 (*n* = 83)

1.5.1 Conditions Resulting in a High Risk of Disease Transmission

1.5.1.1 Overcrowding and Poor Nutrition

(Appendix H: 1-3, 5, 9, 12, 19-21 27, 29, 32-24, 37, 41, 43, 47, 48, 50-53, 55-58, 63-64, 69-71, 73-74, 77, 79-80, 85, 87-88, 91, 94-95, 97-98, 103, 105-109, 113-115, 117, 124-125, 130-131, 136, 138-140, 142, 144-145, 147-151, 155-156, 159-160, 162, 165-166, 168, 170, 172, 176, 178-181, 190, 192-193, 195, 197, 199, 201, 204, 208-210, 212-214, 216-217, 220-221, 224-226, 228-229, 232, 234-240, 242, 247-249, 252-254, 257-258, 261, 263-267, 269, 271-272, 278, 280-281, 285, 287, 289, 293-294, 296-299, 301, 303-304, 306-307, 309, 313, 315-316, 325, 328-329, 331, 339-342, 344, 347-349, 357-358, 360-361; Appendix B: 364-365, 377, 380, 383, 389-392, 396-399)

> One of the most important determinants of health is the absence of war, in addition to good food and adequate housing.
>
> - I.D. Turpie (2008)[49]

In situations of conflict or forced displacement or following natural disasters, the notification rates of TB can increase by as much as 20 times.[50] These challenging situations not only fuel TB epidemics by contributing to poverty and malnutrition but also prevent patients from seeking or obtaining appropriate diagnostics and treatment, which in turn may increase transmission risk.[51] Poor nutrition, overcrowding, and disrupted health services were the most common risk factors reported in 51 articles identified by Kimbrough et al.[50] to support a systematic review regarding the burden of TB in crisis-affected populations. The combination of these crisis-associated risk factors has the propensity to increase active disease progression by contributing to TB reactivation among a pre-existing latent TB population as well as prolonging infectious periods which lead to poor individual outcomes and increase transmission risk.

1.5.1.1.1 Overcrowding

During times of conflict or forced displacement or following natural disasters, populations are often dispersed in temporary shelters, camps, or host communities, which increases community or population density.[50] Overcrowding in refugee camps is well documented, particularly in situations where immediate preparations are required to accommodate an influx of people fleeing conflict. Overcrowding has the propensity to increase the likelihood of exposure to infectious TB, leading to increased rates of LTBI, which may not manifest as active TB cases until months or years later.[50] In the aftermath of the 2011 earthquake in Japan and subsequent tsunami, Kanamori et al.[52] reported on the contact-tracing activities of a particular individual diagnosed with smear-positive pulmonary TB. Crowded shelters were all that were available for evacuees, and the individual had been sharing a 60 m^2 coastal shelter for 3 months with 50 other evacuees. Isolation measures did not exist, and medical staff had not considered the diagnosis of TB, which significantly delayed treatment commencement and may have resulted in TB transmission within the shelter. Of the 50 evacuees tested, 8 were diagnosed with LTBI. An increased burden of LTBI can occur in a crisis-affected population, which has long term effects, whereby complications owing to reactivation of TB disease can occur sometimes many years after the exposure event.[50]

Elevated rates of TB due to overcrowding are not observed only in post-conflict communities or following natural disasters. In a prevalence survey conducted in a remote village in Northern Pakistan where the prevalence rate of smear-positive pulmonary TB (554 per 100,000 population) and smear-negative TB (1,949 / 100,000 population) is remarkably high, overcrowding affected 75% of the study population.[53] In this particular study, overcrowding was classified as three or more people living in one room. Owing to the remoteness of this community and long distance to the nearest health centre and anti-TB medications, only 38% of the cases identified in this study completed treatment. Not only do partially treated pulmonary cases remain a constant source of TB infection in an overcrowded setting but smear-negative patients are also at risk of progressing to a smear-positive status, and all have the potential to promote the emergence and transmission of drug-resistant strains.[53]

The incidence rates of TB are extremely high among the Canadian Inuit and First Nations populations. The incidence rate among Canadian Indigenous populations ranges from 4.7 to 119.2 per100,000 population, which at its peak is 26 times higher than the overall incidence rate of TB in Canada.[54] Among Canadian First Nations communities, being part of an isolated group can increase the risk of TB by as much as 2.5 times, and the combination of lower income levels and overcrowding may further compound the issue.[55] Overcrowding, otherwise known as population housing density, is defined in Canada by the National Occupancy Standards (NOS). The NOS consider a residential dwelling to be overcrowded if one or more bedrooms is required to adequately house the occupants and where adequate occupancy is achieved if each room sleeps no more than two adults or two children under the age of 18 years.[56] It has been reported that an increase of only 0.1 persons per room can increase the risk of two or more cases of TB within a community by 40%.[57] Clark et al.[55] reported that communities with an average of 0.4–0.6 persons per room had an incidence rate of TB of 18.9 per 100,000 population whereas First Nations communities with an average of 1.0–1.2 persons per room had an incidence rate of 113 per 100,000 population.

In a study conducted by Bhatia et al.[58] among Tibetan refugees in India, being a sweater seller or student was significantly associated with higher rates of TB at 1,600 per 100,000 population and 1,110 per 100,000 population respectively. During winter months, Tibetan sweater sellers travel out of refugee settlements to large Indian cities for this seasonal work, which lasts approximately four months of the year. Continuity of care remains a challenge for members of the Tibetan diaspora in India who may be mobile throughout TB treatment and away from

medical and family supports available in refugee settlements.[59] In the absence of protection from Tibetan settlements, Tibetan sweater sellers live in extremely impoverished and overcrowded accommodations where adherence to TB treatment is unlikely.[58] Overcrowded sleeping arrangements also affect students staying in Tibetan boarding schools.[58] Typical sleeping arrangements in Tibetan schools in India are dormitory-style accommodations with poor ventilation. At the time of the study by Bhatia et al.[58], isolation options for infectious individuals such as sweater sellers and students did not exist.

Within long-term congregate settings, one might reasonably expect high rates of smear-positive pulmonary TB; however, smear positivity was reported in only 15–29% of monks in Tibetan monasteries in India where pulmonary disease accounted for 87–91% of diagnoses.[58] Masur et al.[60] reported that microscopy results showed that 53% of slum dwellers with a cough diagnosed with active TB three years after Haiti earthquake were sputum smear positive (culture unknown). Low rates of smear positivity may be attributed to high proportions of unknown results, poor utilisation of laboratory-based services, low quality of available diagnostics, and over-diagnosis of smear-negative TB.[58] While overcrowding experienced by the general population in Tibetan settlements contributed greatly to the rates of exposure to TB among sweater sellers and monks, poor nutrition was also a risk factor for sweater sellers.[58]

1.5.1.1.2 Poor Nutrition

> Intensive research during the past 12 years on the relationship between diet and susceptibility to respiratory infections and tuberculosis has convinced me that the human organism can protect itself against infection virtually completely by proper nutrition.
>
> - B.P. Sandler, M.D. (1951)

Humanitarian crises often result in conditions conducive to TB.[61] Although there are multiple studies investigating the association between TB and nutrition with contradictory findings and inconclusive aetiology, the weight of the evidence favours poor nutrition as an important risk factor for mortality and morbidity due to TB in resource-poor and impoverished settings.[62] Iron deficiency anaemia in various populations has been found to increase susceptibility to TB infection,[62,63] whereas vitamin A has been found to reduce multiplication of cultured bacilli.[64] Notably, zinc[63] and vitamin C[65] deficiencies have been shown to be independent markers of disease severity of TB. Deficiency of selenium, a trace element that maintains immune processes at normal levels, is a particularly significant risk factor for HIV patients at risk of developing TB.[62,66] A cross-sectional study among HIV-positive and HIV-negative patients

with pulmonary TB in Malawi reported that wasting and higher plasma HIV load are associated with micronutrient malnutrition.[67]

It is widely accepted that cell-mediated immunity, as a host defence against TB, is affected by poor nutrition. Indeed, pulmonary TB was historically known as 'consumption' – a wasting disease, as manifested by significant weight loss. In early literature from the beginning of the 20th century, high rates of TB among new recruits to the Norwegian Navy was attributed to overcrowding, poor hygiene, and poor housing.[68] After recruitment, TB rates did not improve after adequate housing and hygiene were implemented. It was only when the diets of naval cadets were fortified with foods high in protein that TB morbidity rates rapidly declined.[68]

Other early 20th century reports suggest that depleted protein intake is closely associated with contracting TB.[68] During the First World War (1914–1918), rationed food including coarsely milled bread (higher in fibre), pork, butter, and sugar improved the dietary intake of many Danes from a caloric perspective.[69] Neutral Denmark exported much of its meat, fish, poultry, and dairy stocks to the detriment of the local population, who were left with a protein-poor diet because protein-rich foods were not rationed.[68,69] During this time, TB rates increased. Then, during the German blockade in 1918, local foods were retained, which increased access to protein-rich foods, and TB rates stabilised, an anomaly not seen in other Scandinavian countries at the time.[70] Prior to the war, incidence rates of TB in Denmark in 1913 were 135 per 100,000 population. TB incidence rates in Denmark peaked in 1917, reaching 176 per 100,000 population; decreased to 138 and 119 per 100,000 population in 1918 and 1919, respectively; and consistently declined well into the 1920s and beyond.[71]

Reports from France indicate that the same pattern was observed during the Second World War (1939–1945) as soon as food rationing began.[71] High rates of severe TB were particularly evident among institutions such as prisons and lunatic asylums, where populations were subject to strict rationing measures. TB cases in French lunatic asylums increased by 50% during the war.[72] In contrast to the general Parisian population, the only conditions that changed during the war in lunatic asylums were food rations.[72] In particular, rations were deficient in lipids and animal-origin proteins but contained a sufficient quantity of vitamin B and C.[71] Another example from the First World War is that the TB incidence rates among members of the Paris fire brigade, who undertook intense and frequent physical activity and were entitled to large and well-balanced rations, remained the same as the rates before the war, in contrast to the markedly increased rates of TB among their compatriots.[73] However, this lack of change in

incidence rates cannot be directly attributed to nutritional status because of other environmental factors associated with this profession such as smoke inhalation resulting in damaged lungs. Diets deficient in both proteins and micronutrients are associated with lowered resistance to infection, which in turn increases susceptibility to and disease severity of TB and delays recovery.[62]

Insufficient dietary caloric intake is also associated with an increased risk of TB. Prisoners of war in Japanese camps had to endure harsh living conditions including a diet that lacked calories and most micronutrients. CXR images of repatriated prisoners often showed radiographic abnormalities such as depleted calcium content of bony structures.[74] Of 1,507 CXR films of prisoners of war reviewed, 7.8% (n = 118) showed pleural or pulmonary disease or both; however, it should be noted that repeat CXR and laboratory confirmation were not available at that time.[74] In an African study, hypocalcaemia was identified in 45% (45/102) of patients diagnosed with pulmonary TB, all of whom had a body mass index <20 which in this study indicated poor nutritional status, and moderate-to-extensive radiographic disease.[75] Other research on a similar theme state that in the nineteenth-century, it was believed that *kumiss* (fermented mare's milk), which is low in fat but high in sugar and vitamins B12 and C, was the most important protective and curative factor against TB in Kazakhstan; this belief persists today among the Kazakh people.[76] Its curative attributes were considered so critical to the absence of TB among the highly mobile nomadic pastoralists of the Eurasian steppe during the nineteenth century that it was eventually included in the Soviet-era medical practice, and its use was supported by some European and American physicians.[76] Mass production, decline in quality, selling of counterfeit products, and abandonment of traditional methods of food preparation nearly rendered the product non-profitable and forgotten, and in 2013, Kazakhstan had the world's second highest rate of MDR-TB.[76] It has been reported that the current epidemic has created an opportunity for contemporary use of *kumiss* and the associated revival of Kazakh culture.[76]

1.5.1.2 Treatment Delay due to Financial Constraints and Health Illiteracy

(Appendix H: 1-2, 4-5, 7, 10, 12, 19, 22, 27, 29-30, 32-33, 48, 50, 52, 55, 59, 63, 69-70, 81, 83-84, 91-92, 94, 99-101, 103, 107, 111-112, 114, 117-118, 121, 124-125, 128, 133, 135, 138, 147, 149, 156, 159-160, 162, 165, 171, 173-175, 180, 182-183, 188, 192, 194-199, 201, 203-204, 213, 216, 219, 224, 227, 232-234, 237-242, 244, 247-248, 254, 256, 259, 261, 264, 268, 271-272, 274-275, 280, 284-287, 291-294, 296-297, 299, 302-303, 308, 311-312, 314-317,

319-321, 325, 329, 331, 334, 340, 347, 349, 351-352, 357-358, 360-361; Appendix B: 365-367, 370, 372, 374-375, 379, 381, 385, 388, 390, 392, 395, 397-399, 402-404)

> Tuberculosis is really not a medical disease.
> We know how to diagnose it,
> we know how to treat it, and
> we know how to prevent it.
> It's a socio-economic problem.
>
> - Dr E. Hershfield, Director of TB Control, Manitoba (North-South Institute 1997:6)

Poverty and illiteracy are both indicators of a low socio-economic status.[77] For many communities in the developing world, severely restricted financial resources leads to numerous limitations, including a lack of access to health care for TB. In addition, a lack of general knowledge about the signs and symptoms of TB, may ultimately prevent poverty-stricken patients from seeking diagnosis and treatment. According to the WHO, a one-month delay of a TB patient commencing effective treatment results in one to two more individuals becoming infected.[78]

Delivering basic services to rural areas is a challenge in many developing countries. Pastoralists are nomadic people with no permanent address, and migration usually occurs seasonally. For many Ethiopian pastoralists, the income relies exclusively on livestock rearing.[79] In inner Mongolia, there are few revenue-generating options in rural areas other than pastoral agriculture.[80] As a result, people living in these rural areas are often disadvantaged by the long distances which are a barrier to accessing health care.[79] Travelling long distances to seek health care either indirectly adds to the cost of health care or is prohibitive for exceptionally poor people.[81]

Among poor communities in a rural area of Inner Mongolia with high TB prevalence, only 60% characterised a prolonged cough as a symptom of TB, and as many as 40% could not identify that close contact with other infected persons was a risk factor for transmission.[81] Owing to financial constraints, individuals in a low-income group with a lower level of education were more likely to avoid seeking health care or prefer basic care provided in the village over established services from more qualified and resourced providers.[81] A larger sample across a wider area of Inner Mongolia displayed an even lower level of knowledge about symptoms of TB, with less than 27% recognising a cough lasting over 3 weeks as a symptom.[82] Of respondents in the study who were health employees, only 18.6% answered all

TB-related questions correctly, which may explain the diagnostic delays.[82] It was reported that 25.4% of participants would visit non-TB-related clinics if TB was presumed; however, the authors did not identify the associations of specific risk groups with specific health-seeking behaviours or the role of village-level health care in their study population. However, the authors suggested that in comparison with the Han Chinese individuals, the Mongolian minority groups in this study population were 1.52–2.18 times more likely to be aware of TB symptoms and curability as well as the location and availability of free TB clinics and dispensaries but less likely to know about the transmission mode.[82]

Treatment delays (from diagnosis to commencement of treatment) of up to 89 days has been reported in one of the Mexican communities close to the US border.[83] Furthermore, a study conducted among patients with TB who identified as Ethiopian pastoralists have attributed significant delays in diagnosis to high illiteracy rates, both scholastically (88.5%) and from a biomedical perspective (64.2%).[84] In this population, a mean delay of 130 days from the onset of symptoms to when the patient presented to a health care provider was reported. However, there was a significant difference in this time delay of 13 days between those with high and low biomedical knowledge, indicating that poor knowledge was directly associated with delays in health-seeking behaviour. The effect of poverty, mobility, and illiteracy on the lack of access to health care in this population of nomadic pastoralists was compounded by a mean distance of 79.2 km to the nearest health facility and limited means of transportation.[84]

1.5.1.3 TB/Comorbidities

(Appendix H: 2, 4, 7, 13, 15-16, 22-24, 33, 43, 48, 51-52, 60, 68, 72, 82-85, 88, 92, 94-96, 102, 108, 110, 114, 116, 121, 125-126, 132, 134, 136, 138, 140-141, 144, 148-149, 151-152, 155, 158-161, 171, 174, 177-180, 186, 190, 192-193, 196, 199, 201-203, 209, 221, 225-228, 230, 234-235, 239, 242, 245, 247-248, 251, 254, 256, 258, 261-262, 267, 271-273, 277, 282, 285, 291-294, 301-303, 306, 313, 322, 325-327, 329, 334-335, 337, 341, 346-347, 349-358, 360-361; Appendix B: 370, 372, 380, 389-390)

> The risk of death is significantly higher in HIV-infected patients with tuberculosis.
>
> - S. Beheshti, University of Medical Sciences, Tehran

The coexistence of TB and other communicable and non-communicable diseases in the same individuals results in opportunistic infections and greater transmission of TB. TB/HIV and TB/diabetes are among the most common comorbidities combinations explored in the present

scoping review; however, all immunocompromised groups and individuals with chronic systemic conditions are at risk of active onset and/or reactivation once exposed to MTB.[28]

The heightened risk is especially pronounced in regions that have a high prevalence of HIV. As many as 1.2 million new TB cases diagnosed and 400,000 TB-related deaths were recorded among HIV-seropositive patients in 2015.[78] In HIV-negative patients, TB generally progresses slowly over many months, with pulmonary TB being the predominant form.[28] However, HIV coinfection causes TB to rapidly progress and results in extensive dissemination in a matter of weeks.[28] Typically, disseminated disease (e.g. miliary TB) resembles millet seeds on CXR images; which is unusually observed in HIV-negative patients.[28] The presence of HIV makes it more difficult to identify TB on the basis of CXR findings and sputum smear microscopy.[85] CXR findings in PWH can be non-specific and requires accurate interpretation by experienced practitioners.[86] When CXR is used as a supporting diagnostic tool, results depend on the severity of HIV disease and the CD4 count, whereby people with more advanced HIV disease are more likely to have non-specific markings or normal CXRs.[86] As immunity declines, so too does the frequency of pulmonary cavitation and smear positivity in patients with TB/HIV coinfection, and an increase in extrapulmonary disease (>50%) and disseminated TB is observed.[28,87]

From a programmatic perspective, it is possible to provide effective TB control programs under challenging circumstances; however, death is more likely with TB/HIV coinfections under crisis situations.[50] This was observed among Indian refugees in the Churachandpur district in India in 1998, where TB was successfully managed in the study population, but patients with TB/HIV coinfection were more likely to die during treatment.[88] From June 1997 to October 1998, Churachandpur experienced civil conflict, population displacement, and interrupted TB treatment services, in addition to an ongoing HIV epidemic.[88] Against a backdrop of random killings and sniper fire, health workers had fled to safety, and drug supplies were erratic. Over 50 villages containing 10 different ethnic groups were destroyed, displacing 13,000 people.[88] Eventually the district TB control program closed, and other community programs such as malaria control and immunisation services were abandoned in rural areas.[88] A year after the TB program had closed, a local advisory group was formed to implement WHO-specific recommendations for post-conflict management of TB using the DOTS strategy.[88] Effective community support, locally sourced outreach workers, and services embedded within local communities enabled 91% of patients to successfully complete treatment with only a 3% loss

to follow-up rate and 3% treatment failure rate.[88] Although 3% of patients with TB died, HIV seropositivity was associated with an unsuccessful treatment outcome; of the 22 TB/HIV-coinfected patients enrolled in the study, 18% died during treatment.[88]

While TB is the leading cause of death from an infectious disease worldwide, diabetes is one of the top 10 causes of death globally.[78] Diabetes affects 387 million people worldwide, and 80% of affected individuals live in low- and middle-income countries.[89] Numerous observational and epidemiological studies suggest that diabetes is a risk factor for the development of active TB[90,91]; however, there is no consensus on the pathophysiological explanations for the association.[92] Suggested explanations include impaired host immunity, micronutrient deficiency (malnutrition), low production of interferon gamma, and pulmonary microangiopathy.[90,93] In any case, developing countries with high TB incidence and increasing rates of diabetes are at increased risk of comorbidities.

In a descriptive epidemiological study comparing rates of diabetes and TB in Saskatchewan Aboriginal and non-Aboriginal people, women aged 50–59 years with diabetes exhibited higher rates of TB regardless of ethnicity.[94] Similarly, no interaction between diabetes and Indigenous status in a large population-based cohort study conducted in Australia has been reported.[95] However, in Australia, a country with low TB incidence, people with self-reported diabetes were 1.5 times more likely to develop TB than those not who did not self-report diabetes. On the basis of this moderate increase in the risk of TB among diabetic patients, the authors suggested that the presence of diabetes is not in and of itself sufficient to warrant testing for LTBI in the absence of other risk factors.[95] In contrast, in Tanzania, where there are more than 70,000 new TB cases per year with approximately half also diagnosed with diabetes, a case–control study identified diabetes as a predictor of pulmonary TB with an odds ratio of 4.23, where age, sex, socio-demographic variables, and serum alpha-1-acid glycoprotein had been adjusted for in HIV-negative patients.[96] As endocrinology and infectious diseases are not typically specialty areas that work together, it has been suggested that integration of these services may assist with preventing the rise of diabetes in TB-endemic areas.[78,96]

Remarkably, studies included in this scoping review did not comprehensively discuss the proximate causes of immune dysregulation associated with non-communicable diseases, which is known to be a strong driver of TB. Comorbidities such as the human T-lymphotropic virus (HTLV) types 1 and 2 and many of the behavioural risk factors associated with TB have been shown to be important in different settings. For example, transmission of HTLV-1 is generally

via blood transfusion, contaminated needles/syringes or via sexual intercourse[97] but increased susceptibility for TB in patients with HTLV-1 has been observed due to a reduction in TNF-α production.[98] HTLV-1 has also been shown to be associated with a history of TB disease[97] and several epidemiological studies in Japan, Nigeria and Brazil have reported a high burden of HTLV-1/TB coinfection.[99-101]

Many studies have shown that atypical comorbidities and certain environments are associated with TB infection and are risk factors for disease progression.[22] Chronic lung diseases such as chronic obstructive pulmonary disease (COPD) and exposure to smoke via wood fires or cigarette smoking increase individual vulnerability, and increase the risk of TB infection.[102] The association between smoking and COPD is well established, and it is increasingly evident that smoke from wood fires and other types of biomass pollutants are dose-dependent risk factors for COPD.[102] A Turkish study investigating the effect of TB on patients with COPD found that TB reduced respiratory function, increased partial pressure of carbon dioxide ($PaCO_2$), and led to unfavourable outcomes such as premature death in these patients.[103] A systematic literature review found that smokers are nearly twice as likely to be infected with and die from TB.[102] In many parts of the world, accessibility to diagnostics for chronic respiratory issues are limited[104] due, in part, to busy referral centres focusing on immediate and acute medical conditions.[22] This problem highlights the need for strengthening primary health interventions and disease prevention initiatives whereby TB control programs could integrate into broader health care systems to provide better care for patients with potential comorbidities that place them at greater risk for unfavourable TB treatment outcomes.[104]

1.5.2 Conditions Resulting in Programmatic Challenges

1.5.2.1 Climatic Conditions

(Appendix H: 6, 11, 14, 38, 63-65, 69, 74, 76, 78, 86-87, 94, 98, 101, 106-107, 109, 112, 115, 124, 131, 134-135, 139, 142-143, 146-147, 152, 155-156, 163, 170-171, 190, 199, 204-205, 210-211, 220, 224, 244, 253, 259-260, 284, 287, 298, 311, 331-332, 342, 345, 349, 357, 361; Appendix B: 363-364, 369, 371, 376, 378-379, 393-394, 401, 404)

> At a global level, we still have a relatively poor understanding of the ecological factors that are driving TB epidemics and what can be done to control them.
>
> - Dr P. Small, Deputy Director Tuberculosis Delivery Program, Bill and Melinda Gates Foundation

It has been established that extreme weather events such as hurricanes and earthquakes adversely affect infrastructure, patient outcomes, and the management of TB; however, climatic and geographic conditions may also affect susceptibility to pathogens.[105] In the pre-antibiotic era, medical officers believed that high altitudes were beneficial for tubercular patients because of the expansion of the lungs at higher altitudes.[106] By the early 1800s, treating patients with TB at sanatoria at high altitudes during winter and monsoon seasons was criticised because elevation makes the already struggling lungs to exert more effort than that required at lower altitudes, which resulted in increased aggravation with repeated attacks of haemoptysis.[106] In some instances, patients with TB retreating to hill stations of India during the summer months were cured on account of greater expansion of pulmonary cells, exercise at high altitudes, and open-air life in an antiseptic environment.[106]

In China, TB is reported to be a seasonal disease.[107] TB prevalence is reported to increase during periods of muggy weather, defined in one study as higher humidity, higher temperatures, more precipitation, and little sun.[108] Geography was also reported to influence an increase in the prevalence of TB in some regions of China, specifically those at a higher elevation, lower latitude, and lower longitude, and mostly located in western and south-western China, including Tibet.[108] Notably, some Tibetans living in exile in India believe that Tibet was a nation free from disease because of its elevation and cold climate and that the erratic climate of India is not suitable for Tibetan bodies.[109]

In Chandigarh, India, national surveillance data over a period of 1 year was analysed. In general, communicable disease morbidity was found to be more prevalent during winter and summer months and less so during monsoon months.[110] Pulmonary TB morbidity in Chandigarh was 4.86% higher during the summer.[110] Similarly, a systematic review conducted between 1971 and 2006 found that rates of TB case notifications peaked during spring and summer seasons in all countries and regions included in the study (South Africa, India, Hong Kong, Japan, Kuwait, Spain, the UK, Ireland, and Mongolia) except southwestern Cameroon and Russia; however, Sharma, Bhatnagar, Goel, Verma and Swami[110] did not provide data identifying potentially influential factors such as geographical coverage, climatic patterns, and socio-demographics. In contrast, a Japanese study has reported increased rates of TB morbidity and mortality during the winter months.[111]

It is reasonable to expect the seasonal distribution of TB to peak in winter months owing to time spent indoors in potentially overcrowded, poorly ventilated environments; however,

although an increase in primary and re-infection cases may be explained by these conducive environments, a tendency to remain indoors during winter does not explain the increase in reactivated cases.[112] The exact mechanism of seasonal distribution remains unclear. Some researchers have suggested that changes in vitamin D levels and impaired host immunological defence explains the reactivation of LTBI during the winter months[113] and several studies have shown an association between low vitamin D levels and reactivated TB.[112] However, while there is some evidence that shows that veiled clothing was significantly associated with low vitamin D levels,[114] it is unclear whether veiled women are more likely to experience TB reactivation when compared to unveiled women of the same culture. Many studies investigating seasonal TB show no significant difference in TB rates between genders.[112]

Overall, seasonal patterns and distribution of TB morbidity and mortality differ greatly across populations with varying climates and landscapes. An increase in TB rates in winter months may be a result of other pathogens, such as the influenza virus, that do not cause TB but may contribute to disease manifestation or progression in patients.[112] Increased TB notification rates in spring and summer months may be associated with transmission occurring during the winter months but progression to disease occurring in spring and summer months. A tendency to remain indoors, coupled with less airflow, less ultraviolet light exposure, and malnutrition due to lower availability of food and sufficient nutrients during winter months in some countries, may accelerate disease manifestation and progression in some populations.[112] Moreover, individuals with presumed pulmonary TB may be reluctant or unable to seek health care in the winter months or may wait until symptoms are severe, and these diagnostic delays may explain the increased rates in spring and summer in some populations.[112]

1.5.2.2 Geographical Challenges

(Appendix H: 6, 10-12, 31, 35, 40, 50, 62-63, 70, 84, 86, 101, 106-107, 112-113, 120-121, 126, 135, 137, 147, 154, 157, 163, 171, 173, 187-188, 197, 205, 233, 262, 281, 288, 292, 295, 305, 310, 317, 323, 349, 358,361; Appendix B: 363-364, 366-367, 369, 372-374, 376, 378-379, 381-384, 388, 391-394, 397, 399, 401-402, 404)

> The place where an individual lives or works should be considered as a potential disease determinant.
>
> - R.S. Kirby, E. Delmelle & J.M. *Annals of Epidemiology*; 2016: 1-9

In addition to their effect on TB infection and disease, weather and geographical conditions adversely impact supply and delivery chains. In some Canadian Arctic Inuit communities, winter months impede the delivery of specimens to the laboratory in a timely manner. White-outs, common in winter months, effectively ground the aircraft used for specimen transportation in remote area outposts inaccessible by road or snowmobile, and the turnaround time from sample collection to receipt in the laboratory may increase from the usual 2 days to 10 days.[115] The consequence of delayed diagnostics is the risk of exposure to other people, the requirement for people to remain in isolation longer and delays in the commencement of effective TB treatment.[116]

Mountainous terrains pose significant challenges to TB management. In mountainous provinces in China, full adherence to the national guidelines for the management of TB has been difficult to achieve.[117] In Yunnan, a mountainous province of China that is home to 44 million people, poor transportation options affect TB control.[118] Travel on foot is one of the few options; however, 50% of the population lives at a distance of more than 40 km from a doctor.[118] A descriptive study found that there was a mean diagnostic delay of 71 days for smear-positive patients with pulmonary TB receiving care at a TB centre, and it was associated with geographical distance to health care.[118] Although provision of more local TB centres may reduce delays, it is often not feasible owing to a lack of funding and human resources for health.[118] To overcome geographical challenges in remote mountainous regions of Nepal, NGO-funded outreach microscopy camps have been trialled. While treatment completion rates improved, the yield for active TB case finding did not; moreover, as the health service is under-funded in Nepal, such a program would be difficult to continue as it was resource intensive, unsustainable, and prohibitively expensive.[119]

Distance to treatment delivery points and the burden of having to cover daily costs during the intensive phase of treatment are prohibitive.[79] In a poor, remote area of China, non-compliance is often due to poor transportation, long distances to clinics, wide dispersal of the patient population, and hardship associated with the financial outlay required to manage side effects.[120] In nomadic groups in the Somali region of Ethiopia, nomadic pastoralists, who are dispersed over a large geographical area, prefer traditional medicine and – when traditional medicine is ineffective – religious remedies (reading Koranic verses) over ongoing TB treatment.[79] Geographical challenges were also observed in war-torn Afghanistan. Afghanistan is bisected by high mountain, and accessing health services is challenging. Unlike China and Nepal,

Afghanistan has overcome some of these geographical challenges with substantial assistance from the international community and achieved successful implementation of DOTS within pre-existing health care centres.[121] From 2004 to 2006, the geographical coverage of DOTS in Afghanistan increased 10-fold and the number of patients diagnosed and treated for TB increased by 380%.[121]

Although the potential impact of geographical challenges on a TB control program is a significant issue, the paucity of relevant studies available for this scoping review demonstrates a research gap.

1.5.2.3 Damaged Health Infrastructure and Limited Human Resources for Health

(Appendix H: 1, 5-6, 13, 25, 29-32, 46-48, 51-53, 55, 58, 65, 70, 73, 76, 78, 80-81, 83-84, 96-97, 101, 103-104, 107, 110-111, 113-115, 117, 120-121, 125, 129131, 134-135, 137, 139, 141, 143-144, 149, 151, 153-160, 162, 166, 169, 172-173, 176, 184-189, 192-194, 200, 205, 208-210, 214, 224, 228-230, 232, 234, 240, 247, 249, 254-255, 263, 266, 271, 275, 279-281, 287, 291, 294-295, 297, 303, 307, 311, 317, 323, 325, 327, 331, 334, 337-340, 342, 349, 351-352, 357, 361; Appendix B: 362-363, 365-367, 370-372, 374, 379, 382, 390, 392, 404)

> It would seem hardly surprising to anyone that immediately following great destruction of cities and mass migration of peoples, that tuberculosis would take an upward trend.
>
> - G.R. Carpenter. *Medical Bulletin of the U.S. Army*; 1950: 21-34.

In the aftermath of natural disasters, damage to health infrastructure often results in diminished laboratory capacity, decreased staff availability, shortages of medical supplies, and increased distance to functioning treatment facilities. This creates a short-to-medium–term crisis regarding provision of services for patients and health care providers alike. In August 2005, Hurricane Katrina, reached landfall in New Orleans in Louisiana, USA and as a result, nearly 2,000 people died, hundreds of thousands were displaced and there were 130 known TB cases without medication.[122] Flooding forced the Louisiana TB Control Program (LATB) to abandon its headquarters including the state's TB medication stock and TB laboratory facility.[122] Half the LATB staff left the state or were temporarily displaced.[122]

The situation is exacerbated in areas that were medically underserved prior to natural disasters as they predominantly bear the brunt of inadequate treatment facilities post-event. In January 2010, the Haiti earthquake killed over 210,000 people and left 1.5 million people homeless.[123]

In June 2013 – 3.5 years after the earthquake – approximately 279,000 internally displaced people (IDP) remained living in one of 352 tent camps.[124] In the epicentre of the earthquake – 25 km from Port-au-Prince – government buildings, health care centres, many clinics, two of the largest TB sanatoria, the only inpatient treatment facility for MDR-TB, and the building that housed the National TB Program (NTP) were destroyed.[125,126] One of the only public health buildings remaining intact post-earthquake was the National Laboratory, where technicians were retrained to provide diagnostics for some notifiable diseases but not TB owing to capacity issues.[126]

The preoccupation with personal wellbeing often hampers the human response to natural disasters[127]; however, this was not the case in either Haiti or New Orleans. Before the 2010 earthquake, Haiti had over 14,000 TB cases nationally.[128] Intense efforts to locate patients with TB without medication who were dispersed in camps and slums were attended to by non-government organisations (NGOs) and provided with technical experts and local field response teams from the NTP, who quickly regrouped despite the lack of a central building. Within 3 months after the earthquake, 67% of patients in the Port-au-Prince area had been located and were back on treatment, with a further 30% feared dead.[126] Laboratory capacity was weakened by damage to infrastructure and loss of life of laboratory staff.[129] In such situations, the benefits of using diagnostics that may be less sensitive but easier to implement could be worth considering. For instance, oral swabs used as a point-of-care test may assist with identifying those with the greatest risk of being infectious.[130]

In the aftermath of the earthquake, Haiti went from having no national molecular testing laboratory for TB to having a reference public health laboratory in 2012, followed by multiple laboratory services located in tertiary hospitals, departmental hospitals, and primary health care facilities.[129] In New Orleans, despite the LATB running at half their staffing capacity, many evacuated staff contacted an alternate LATB office established 100 km from New Orleans to provide their most recent patient lists.[122] Staff on the ground manually searched shelters and checked locations known to be frequented by patients before the hurricane. By September 2005, all 130 patients had been located and were back on treatment (where applicable).[122]

While natural disasters may be destructive, local communities, national government agencies and NGOs (national and international) work together to re-establish services as soon as possible. In contrast, conflict events do not affect health care systems and TB programs in the

same way. This is because conflict events are usually protracted, and diminished resources can continue over a longer period of time.

Conflict in East Timor and Kosovo disrupted NTPs and severely limited the available human resources for health. In contrast to the efforts in Haiti and New Orleans, both countries struggled to regain order, particularly during their respective early emergency phases. In 1999 in East Timor, groups opposed to referendum results in favour of independence destroyed up to 70% of infrastructure in almost every town and village. Health facilities and government buildings were targeted, and consequently the health care system collapsed.[131] Many staff fled the conflict or were left unable to work. Within a month, approximately 100 international NGOs (INGO) arrived, but the absence of government leaders and mass displacement of the population led to uncoordinated relief efforts.[131] During the emergency phase, most INGOs did not consider TB to be a major problem despite the high reported rates, and resources were directed to other communicable diseases.[131]

In the Balkans in 1999, Kosovo was embroiled in a bloody fight for independence from Serbia and Montenegro (formerly Yugoslavia). This was the result of 10 years of oppression experienced by local ethnic Albanians, who in 1989 had been removed from government positions in health care administration and education after the Yugoslav Government abolished autonomy for Kosovo.[132] Military resistance led by the Albanian-backed Kosovo Liberation Army in 1999 resulted in hundreds of thousands of ethnic Albanians, who had been living in internally displaced person or refugee camps for a decade, returning to Kosovo. Many of these former citizens would reclaim their previous posts and functions in official institutions, previously controlled by the Serbs.[133] During the 1999 conflict, health infrastructure, including health facilities, laboratories, anti-TB medication dispensaries, and the buildings of the Institute of Public Health, were severely damaged.[132] The shift in the balance of power during both conflict and post-war phases placed ethnic minorities, including Serbians, in a particularly vulnerable position, with few attending Albanian-led health services for fear of retaliation, intimidation, and violence.[132]

Management and control of TB in East Timor and Kosovo during their respective times of conflict and post-conflict differed; nevertheless, no strategy used was particularly effective in the short term. In the absence of an NTP in East Timor, there was no coordination, management, or follow-up for TB patients. Some INGO medical officers prescribed their own preferred TB drug regimens, and many local health providers placed patients on single-drug

treatment regimens using drugs obtained from government health repositories before the conflict or using imported anti-TB drugs.[131] Non-standardised drug usage was of particular concern, and many INGOs and local health providers ignored previously adopted international treatment standards. The provision of correct TB treatment increases the likelihood of favourable treatment outcomes such as cure and decreases the likelihood of progression to drug-resistant TB.[134] In 2000, it was decided that the Norwegian NGO Caritas would lead the NTP in East Timor, and the program would be based on the WHO DOTS strategy.[135] However, efforts to improve the integration of health services, increase laboratory capacity, and engage in active case finding did not significantly reduce the levels of TB in the country.[135] Challenges experienced by Caritas included reluctance of government health staff to commit their time to an INGO because they feared job insecurity; consequently, in some instances, experienced TB staff were moved into non-TB roles, and non-experienced staff were trained in TB management.[131]

Although a laboratory network was established by Caritas, smear microscopy was not used in most areas, which led to decreased notification rates of smear-positive cases and increased rates of smear-negative cases. In the district where it was mostly used, an unusually high error rate was discovered during quality control activities, which was attributed to colour-blindness in a laboratory technician.[136] In addition to a lack of microscopy and delayed recognition of colour-blindness in laboratory staff, underdiagnosis of smear-positive cases was thought to be associated with untrained staff performing diagnostic and screening procedures.[136] Obstacles to effective DOTS was associated with high travel costs for patients traversing over mountainous terrains – especially during the wet season because of extreme weather conditions – and insufficient health service provision funding.[137] Case detection rates including smear-positive cases did not improve until 2009 when East Timor's NTP (no longer managed by Caritas) received Global Funds grants.[135]

Similar to the response in East Timor, in Kosovo, an NGO was assigned the responsibility to manage the TB control program, and Doctors of the World USA (DOW) initiated programs for the Albanian majority and ethnic minorities.[138] Due to ethnic segregation, the DOW program worked alongside but not within the Albanian health system in an attempt to bridge gaps between and collaborate with all ethnic groups. Unlike TB control imperatives in other post-conflict zones where morbidity and mortality rates of TB are high, DOW initially adopted a passive rather than active case finding approach but reported that case notification rates

increased by 16% in one year.[132] DOW also appointed a minority clinician and provided training to minority nurses and doctors in TB management and DOTS, led TB education campaigns, and assisted in an advisory capacity with the development of an NTP.

Challenges faced by DOW included ad-hoc delivery of DOTS, particularly in rural areas where it was difficult for senior DOW staff to oversee program implementation in minority areas; inconsistency in reporting; the ability to track a highly mobile patient population that frequently crossed the border into Serbia during periods of inter-ethnic violence; and the reluctance of some nurses to be involved in TB education campaigns in addition to their standard duties, as no additional monetary compensation was made available.[132] Furthermore, many minority doctors felt insecure delivering sputum specimens to the main laboratory within the Albanian-led health care system and instead travelled great distances to use alternate laboratory services.[132]

Reluctance to engage with the Albanian health service was a common occurrence, and some minority clinics sought anti-TB medications from Serbia instead of from Kosovo's main stockpile in the capital Pristina.[132] Serbian drugs did not conform to international standards and supplies were erratic, placing patients at risk.[132] A significant limitation to DOW's minority project was that it focused on Serbian enclaves in the centre of Kosovo and IDP camps, leaving minority groups in isolated regions without access to health care. While Doctors of the World[132] purport that equity to TB services increased for ethnic minorities, many minorities reported reluctance to seek treatment within the major Albanian-led health care system.[133] The aim of any NGO TB program is to eventually subsume into the NTP; however, patient concealment of TB for fear of discrimination and a perceived lack of confidence in the quality of care provided by national health services remains a concern.[132,133]

1.5.2.4 Insecurity and Treatment Interruptions

(Appendix H: 1-8, 13-14, 18, 21, 25, 27, 29-32, 38-39, 42, 44-45, 47, 51-53, 55, 59, 61-62, 65-67, 69, 73-75, 78-80, 83, 85, 89, 92, 95, 99, 101, 103-104, 106, 110-111, 114-117, 119, 121-125, 128-131, 133, 135, 137-139, 141, 144, 147, 151-156, 159-160, 162, 164, 166, 168-169, 172, 174, 176, 180, 184-186, 188-189, 192-194, 197-203, 207-209, 212, 223-224, 227, 230, 233-235, 237-238, 240, 242, 246-249, 251-252, 254-255, 257, 259, 263-266, 270-271, 273, 277, 280, 283-285, 287, 290-294, 297, 299, 302, 304, 306-307, 309-310, 312-313, 315, 317,

321, 323-327, 331, 334, 336-337, 339-340, 342-344, 346-352, 354, 357, 359-360; Appendix B: 362-363, 366, 368-371, 375, 377, 379-382, 387, 389-391, 394, 397-399, 404)

> Understanding and awareness that fits with existing cultural norms and beliefs, and which is sensitive to the level of education of the majority of the population in the area, are key factors in adherence.
>
> - T. Diefenbach-Elstob et al. *BMC;* 2017: 17:70

Many of the barriers to a functioning TB control program are caused by insecure environments. Insecurity because of poverty, conflict, political turmoil, loss of homes, roadblocks/check points, clan fighting/tribal wars, and overall lawlessness in society leads to treatment interruptions for patients with TB, hampers DOTS efforts, and in severe cases, renders a TB control program unable to function.[139] In South Sudan, for example, a protracted civil war killed two million Sudanese people and left 4.5 million displaced. Local health care staff fled; roads were inaccessible or non-existent; and relief supplies including medical and food, had to be flown in, which further amplified the state of insecurity for local communities.[139] In such complex emergency situations, TB services are almost exclusively run by NGOs with the assistance of locally trained staff.[139]

Insecurity can cause mass displacement, limits civilian access to health services, and limits movement of personnel and other resources.[140] Between 2008 and 2010, there were 160 security incidents in Somalia in areas where NGO were present, including 56 shootings and 18 bomb attacks.[140] NGO TB control program efforts are often restricted to specific areas without a possibility of expanding DOTS programs or providing outreach services owing to security issues.[49] Insecurity also prevents NGO staff from travelling outside designated project locations to trace patients who may have missed doses.[140] In regions with ongoing local conflicts, inventory management is challenging and NGO planning of medication and medical equipment delivery to isolated areas is hampered by constant disruptions to communication and transport infrastructure.[141] Insecurity also places staff, vehicles, equipment, and medication stocks at risk, which may lead to a reluctance of NGOs to implement TB control programs in high-risk environments.[141]

While NGOs such as Medicins sans Frontiers (MSF) work in many fragile and insecure nation-states, they withdrew more than 1,500 staff from Somalia in 2008 and again in 2013 because of attacks and death of 16 staff members.[140,142] Bodiang[143] states that within unstable environments, TB control programs should always have a contingency plan in the event of

insecurity which may require evacuation or repatriation. Repeated evacuations of NGO staff in South Sudan are often necessary, with the duration of NGO staff absence ranging from two weeks to longer durations.[139] During evacuations of humanitarian aid staff, the likelihood of treatment interruption is high. Under these circumstances, the ability of NGOs to provide TB treatment at all must be carefully considered.[139] In South Sudan, MSF mitigated the risk of TB treatment disruption by providing patients with 'runaway bags' containing one month's supply of TB anti-medications.[139] As part of their security plan, MSF also establish pre-arranged locations to meet local staff and patients 4 weeks after evacuation.[139] While there are concerns about unsupervised distribution of rifampicin in the community, in many instances, local staff have been reported to remain to oversee treatment.[139]

Many authors have expressed concern over whether TB control programs should be implemented in insecure environments, including refugee camps.[139,140,144-147] Uncertainty regarding the duration of stay of refugees, especially nomadic refugees, in camps may be problematic for TB control programs, as treatment generally requires at least a 6-month commitment.[146] Refugees are often transient because of insecurity[148] and mobile owing to labour work seeking behaviour.[149] The focus on identifying smear-positive patients in refugee camps and other challenging settings to reduce community transmission is often a programmatic priority, and the benefit of establishing TB control programs is generally believed to outweigh the risks.[144,146,150] In countries where the TB burden was high under pre-crisis conditions, and where health services were disrupted during a crisis event, interruption or discontinuation of TB treatment, particularly during the early intensive phase of treatment, may have resulted in relapse of active disease and promote drug resistance.[151] Persistent TB treatment interruption and loss to follow-up may increase the risk of community transmission of active pulmonary disease, which is heightened owing to greater opportunities for repeated exposure in precarious settings.[50,152] In such situations, alternative strategies to DOTS might be considered that promote adherence and meet the overall therapeutic objectives, even if adherence isn't directly confirmed via in-person monitoring.[36]

Working in labour camps to earn money is appealing to some refugees as observed in a Sudanese camp for Ethiopian refugees in the early 1980s. In the post-emergency phase, the World Food Programme stopped providing dry rations, and additional sustenance was not provided for patients with TB.[149] During the transition to a post-emergency phase although security may overall improve, TB treatment can still be jeopardised by communities seeking

to subsist. Despite being aware of the risks of interrupted treatment, numerous male Ethiopian refugees chose to stay in labour camps for extended periods to provide for their families.[149]

In the post-emergency phase, there can be challenges associated with the handover between NGO services and the NTP, in which patient compliance to TB treatment can be directly impacted.[146] In a Somali camp in the early 1980's, all TB patients completed the intensive phase of treatment, however, interruption of TB treatment in the later continuation phase was not uncommon.[146] Reasons for treatment interruption or poor compliance in a Somali camp for Ethiopian refugees included loss of interest (feeling well), transfer to other camps, inability to attend clinic because of poor health, social reasons (such as weddings or festivals), and adverse effects of treatment.[146] In the Somali camp, persons who missed at least three days of treatment were actively traced; however, in the Sudanese camp, limited resources were available for clinic staff to make concerted efforts to track down patients.[146,149]

Unfavourable treatment outcomes have also been observed among 26 Ethiopian refugee camps between 2014 and 2017 for Sudanese, South Sudanese, Somalian and Eritrean refugees, in which 8% of TB patients were lost to follow-up and there were sufficient resources to trace patients.[153] Most studies included in this review report similar reasons for treatment interruption as those observed in Somalia and Sudan, with a few contextual differences. In South Central Somalia, reasons for treatment loss to follow-up included extended periods away from family (as treatment is provided in one location because of insecurity), nomadic pastoralist practices preventing consistent access to healthcare, and the need to return to graze land.[140]

Globally, a multitude of methods are used to manage TB treatment interruption in different settings. Owing to security risks for patients and staff, patients with TB are accepted into the treatment program in South Central Somalia if they agree to staying at the project location for the duration of their treatment. Those without relatives in the area are offered accommodation in a 'TB village' provided by an NGO.[140] Where possible, patients with TB nominate a guarantor who can be reached by telephone for tracing persons lost to follow-up.[140] In Somalia, respiratory isolation is not an option; therefore, patients must find their own accommodation and agree to commit to staying there for the duration of DOTS.[49] In post-conflict Cambodia, free food incentives and mandatory admission for patients with TB mitigate the risks associated with persons lost to follow-up, political insecurity, and costs associated with travel.[154] Community health workers providing home-based DOTS in Afghanistan have contributed to

low rates of persons lost to follow-up.[121] During low-level conflict in Churachandpur, India, community elders were asked to nominate two people per ethnic group to become part-time community outreach workers to deliver DOTS to 10 ethnic groups in the region.[88] With outreach workers living in the same communities as patients with TB, language barriers were avoided, and because workers were never more than 6 km away from patients, absenteeism during allocated DOTS times was a rarity.[88] Other supportive strategies such as using an NGO to access villages during peak times of conflict, thrice-a-week fixed-dose combination treatment regimens to reduce the amount of travel required in a conflict zone, and an incentive program involving distribution of eggs to families to encourage patients to remain in the area were implemented.[88] Lost to follow-up was mainly observed in patients who chose to return home post conflict to find work and support their families.[88]

1.5.2.5 Disrupted Health Services

(Appendix H: 1, 3, 5-6, 12-14, 21, 25, 28, 31, 38, 43, 45, 51-53, 55, 58, 65, 73, 78-80, 83, 97, 99, 101, 104, 107, 115, 119, 121, 128, 130-131, 134, 139, 150, 152-153, 155-156, 159-160, 162, 168-169, 172, 184-186, 189, 192-193, 198, 200, 208, 210, 213, 221, 224, 229-230, 232, 234, 247, 249, 254, 257, 283-284, 294, 303, 306-307, 315, 323, 327, 331, 337, 340, 342, 347-348; Appendix B: 362-363, 369, 371, 375, 379-380, 391, 397, 399)

> Of all the diseases that flourish in the festering communities left in the wake of a modern war, tuberculosis is the most widespread and the most tenacious; its effects will continue to be felt for many years after other epidemics have ceased.
>
> - M. Daniels. *Public Health* 1947; 61: 35-36

Unexpected epidemics may disrupt health services as much as conflict and natural disasters. The 2014–2015 Ebola virus disease (EVD) crisis in West Africa rapidly and profoundly affected Liberia, Sierra Leone, and Guinea Bissau, and health care resources were redirected to fight EVD.[155] The outbreak resulted in deaths of health workers, closure of clinics, disruption of HIV testing and Bacille Calmette Guérin (BCG) vaccination, closure of borders, mandatory curfews, and decrease in outpatient presentations.[156]

The EVD response limited funding available for TB prevention and control strategies in West Africa and resulted in lower numbers of donations for high-prevalence diseases including TB.[157] Although there was a 2.3% increase in Global Funds for TB in 2014, making USD 13 million available, the allocation to Sierra Leone and Liberia was low and prevented adequate

TB treatment supply.[155] Of the three countries profoundly affected by EVD, only Guinea Bissau had sufficient Global Funds allocation to maintain some TB treatment supplies.[155] Disruption of transportation routes limiting drug therapy supplies was particularly evident in parts of Sierra Leone and Liberia.[155,156]

Health systems of affected countries were debilitated, and clinical management of current and prospective TB cases was disrupted. In some cases, particularly in Guinea, hundreds of primary health clinics were closed, leaving patients with TB without access to DOTS.[155] In Sierra Leone, despite clinics remaining open, many patients boycotted health services or discharged themselves for fear of EVD transmission.[155] Impaired functionality of health services almost certainly contributed to missed diagnostic and treatment opportunities as well as preventable TB deaths in the region.[155] Failure to deliver TB treatment regimens to patients in West Africa during this period may also have increased both drug-sensitive and drug-resistant TB strains; however, the impact of treatment interruption and limited access to services may not be realised for many years to come.[155]

Early estimates using mathematical modelling suggest that, as a result of redirected resources to contain EVD, TB treatment coverage was reduced by up to 50%.[156] This estimate did not take into account the disruption of public health campaigns and childhood vaccination programs, including the BCG vaccine.[156] Overall, it is estimated that EVD caused 11,310 deaths in 2014–2015,[78] whereas TB killed an estimated 11,900 people in Sierra Leone, Liberia, and Guinea in 2014 alone.[158] It is difficult but important to weigh the risks between highly prevalent existing infectious diseases such as TB and emerging infectious diseases to epidemic levels.

Unlike the EVD outbreaks of West Africa, the COVID-19 pandemic caused disruption on a global scale and effectively steered the management and control of other deadly infectious diseases off course.[159] During the pandemic, and particularly early on, an increase in TB deaths was observed for the first time in over 10 years which was representative of high numbers of undiagnosed and untreated TB cases.[2]

There are patient and program specific similarities between TB and COVID-19 including the route of transmission, the impact of overcrowding on transmission risk, the presence of cough and fever in some people, the use of Xpert to diagnose disease in some people, a heightened susceptibility to infection for immunocompromised people, and a vaccine that is partially

effective at preventing hospitalisation and death.[159] However, it is partially because of these similarities that efforts to maintain control of TB have faltered in many parts of the world since 2020.

One of the earliest mitigation strategies against COVID-19 transmission in 2020 was widespread lockdowns. In many countries, the intensity of the COVID-19 waves of disease forced health services to redirect staff to assist with the public health response. Staff working in infectious diseases units before the pandemic were filled with experienced contact tracers, and these staff became the most prized human commodity in addition to epidemiologists and laboratory technicians in the early days of the pandemic. The consequences of both lockdowns and reallocation of staff were reduced outpatient care including BCG clinics and a decrease in TB case detection.[160]

The pandemic also changed care pathways in some parts of the world. In the United Kingdom, the program deprioritised treating LTBI cases and TB services temporarily closed in China.[160] In Queensland, Australia, the presence of cough and fever precluded access to primary health care services and instead required symptomatic patients to present to tertiary facilities or book a telehealth appointment. Pre-pandemic, patients with signs and symptoms of TB would be funnelled into the appropriate diagnostic care pathway however, severely diminished services, media saturation, the impact of COVID-19 on the global population's normal activities of daily living, global COVID-19 case numbers increasing by the tens and even hundreds of thousands each day, meant that TB was no longer a differential diagnosis in many parts of the world. This global diagnostic delay has resulted in millions of undiagnosed and untreated TB patients.[2] We are yet to see the full impact of increased numbers of TB infection as a result of increased community transmission during the pandemic.

1.5.2.6 Access

(Appendix H: 2-4, 6-8, 12, 14, 17-19, 30-31, 44, 50, 52, 55, 59-63, 67, 70, 75, 80-81, 83, 91-92, 94-95, 97, 99-103, 107, 110, 112-116, 118-121, 124-125, 129-130, 133, 135, 137, 139, 142, 144, 147, 149, 152, 154-157, 159, 162, 165, 167, 172-174, 179, 185-188, 192-194, 196, 202-203, 205, 208, 210, 213, 216, 219, 221, 224-225, 233-234, 238-240, 243, 247, 249, 252, 254-257, 262, 265, 268, 271, 279, 282, 284-286, 291-293, 295, 299-300, 303, 307, 310, 312, 314, 316, 319-320, 323, 325, 327, 330-331, 333-334, 337, 339, 342, 347, 349, 352-353, 357-358, 360-361; Appendix B: 362-367, 369-381, 383-384, 387, 389-391, 394-395, 397-398, 401-402)

> 400 million people do not have access to essential health services. The world's most disadvantaged people are missing out on even the most basic services.
>
> - M. P. Kieny,[154] Assistant Director General, Health Systems and Innovation

While conflict, natural disasters, and pandemics all impact TB programs, so too does limited access to health facilities. Residents of remote or inaccessible areas, nomads, and highly mobile populations experience hardship owing to access issues or, more precisely, the lack of access to health care facilities. For example, an estimated 70% of the Afghani population lives in sparsely populated, hard-to-reach areas. These scattered communities are often located in harsh mountain ranges, with many enduring 50°C summers and sub-zero winters.[162] Afghanistan has some of the worst health statistics in the world with poor standards of living[121] and the highest TB burden in South Asia.[163] The NTP of Afghanistan has been in a state of crisis since 1979 because of decades of conflict.[121] Afghanistan did not have a TB control program for 10 years between 1981 to 1991, with some medical supplies and TB treatment available between 1991 to 1994.[164] The terrorist attacks on the USA on 11 September 2001 rapidly escalated humanitarian issues for the Afghani people due to widespread withdrawal of both technical assistance and funding from international organisations.[164] With 60–70,000 new TB cases per year[165] and an incidence rate of 333 cases per 100,000 population, the total collapse of the Afghani NTP in 2001 coupled with climatic and geographical difficulties, led to monumental TB control challenges.[121] When the NTP was obliterated by conflict, only 14% of Afghanis had access to DOTS,[165] and basic health services such as BCG vaccination[164] and contact screening were no longer available.[166] Efforts by individual NGOs to establish TB clinics in Pakistan/Afghanistan border areas failed to meet global targets for detection and cure.[164]

The situation in Afghanistan began to improve when TB was declared a national priority in 2001.[42] Government commitment and international recognition of a serious TB problem in Afghanistan enabled the re-establishment of the NTP after 2001 which was linked in with the country's basic health services package.[167] The Ministry of Health in collaboration with several international partners, re-established and restructured the NTP and divided the country into 7 regions and 34 provinces to improve TB management.[42] In 2004–2005, TB diagnostic capability was rapidly expanded with 600 microscopy units, and delivery of DOTS occurred in over 1,000 primary health facilities.[168] From 2001 to 2005, the number of health facilities providing TB services grew 10-fold, and the number of smear-positive pulmonary TB cases detected increased by 380%.[121] A decade later, 96% of the population had access to DOTS[168] and contact screening was introduced, with a yield of 723 cases per 100,000 population.[166]

Unlike most other countries, women and girls bear a disproportionate share of TB burden in Afghanistan, likely owing to cultural-based gender biases; thus, the employment of a predominantly female community-based DOTS workforce and female physicians enabled increased access for women and girls.[42,167]

While it is generally agreed that community-based DOTS is an effective strategy for patients to be able to access long-term treatment,[134] it is not a one-size-fits-all solution. As DOTS requires a treatment of minimum of 6 months under direct observation, treating migratory or nomadic people presents particular challenges to TB management. The nomadic pastoralists of sub-Saharan Africa are reportedly difficult to observe directly during treatment as they often reside in extremely remote areas and may traverse thousands of kilometres seeking pasture and water for their livestock.[169] Much of the land traversed is located in desert areas such as the Sahara or in semiarid areas such as the Sahel region, where health facilities are few and far between. Clan boundaries, which are generally respected, further impede access to health facilities.[169] While many pastoralists incorporate self-preservation measures such as avoiding areas infested with disease vectors and avoiding communities with measles outbreaks, they also actively transmit diseases including TB, to settled populations as they move through populated regions, adding to the risk of disease dissemination.[169]

The cornerstone of any effective TB control program is rapid diagnosis to ensure commencement of treatment and mitigation of transmission risk. A study on Ethiopian pastoralists found that in some cases, patients experienced delayed access to healthcare and subsequent diagnostic delay of more than two years owing to poor knowledge of symptoms and distance from health facilities.[84] In a rural area of Nepal, Yamasaki-Nakagawa, Ozasa, Yamada, Osuga, Shimouchi, Ishikawa, Bam and Mori[170] reported a 3-month waiting period for TB diagnostics. In this study, diagnostic delay was found to be more pronounced among women, who often chose to visit a local traditional healer, resulting in an average diagnostic delay of seven months.

While health facilities are available in many settled populations that nomads pass through, disease control programs often fail to have an impact on migratory populations. From 1985 to 1990, 90% of Somali nomads did not have access to national health programs.[169] An estimated TB prevalence of 4.6% in adults across three nomadic pastoralist populations of Chad[171] suggests that a participatory approach is warranted for community health workers from nomadic communities to receive basic training and be equipped with medications to prevent

the transmission of TB. It is reported that 86% of the Abagusii people, a pastoralist community of southwestern Kenya, preferred self-treatment over seeking care from health professionals[172]; therefore, this approach, together with training in active case finding and working with traditional healers, has potential.

1.5.2.7 Allocation of Financial Resources

(Appendix H: 5, 10, 12-13, 23, 26, 30-32, 35, 41-42, 44, 48, 51-52, 55, 73-74, 76, 80-81, 83, 92, 97, 99-100, 103, 106-107, 111, 113-114, 116-117, 119, 121, 125, 128-129, 138, 141, 151, 153, 155-158, 162, 171-172, 174, 177, 180, 185-188, 192-194, 199, 206, 208, 214-215, 222, 224-225, 227, 229-230, 232-233, 238, 240-241, 244-248, 251, 254, 262, 265, 268-269, 271, 275, 282-283, 286-287, 291, 299-300, 302-304, 306-307, 309, 311-313, 317, 321, 324-327, 331, 334, 336-338, 340, 343-347, 349-352, 354-361; Appendix B: 365-366, 377, 380-382, 390, 392-393)

> The political instability and economic difficulties of developing countries should not relegate the tuberculosis control effort to second place.
>
> - J. M'Boussa., D. Yokolo., B. Pereira., S. Ebata-Mongo. *International Journal of Tuberculosis & Lung Disease* 2002; 6: 475-478.

There is a growing gap between available international funding and funding required to achieve the targets of the End TB Strategy.[78] Where there is merit in using project-specific approaches to acquire short-term funding, there are broader funding opportunities and partnerships available.[173] Although not available across all regions, in-kind support from institutions results in new financing, technology, or training opportunities, which enables expansion and scale-up of TB control programs.[173] In complex and fragile states, international funding and administration supports TB control, but leadership and knowledge of the consequences of TB at a national level is crucial.[174]

Where fragile states are financially supported by NGOs, one of the challenges is determining the most appropriate time to transfer responsibility for healthcare to newly formed or reinstated governments. In Cambodia, the regime of the Khmer Rouge included the genocide of the majority of health professionals in the country, and only several dozen doctors remained when the government was defeated in 1979.[175] The health infrastructure was left heavily depleted; over the following years, there were a number of unsuccessful partnerships for TB management with the French Red Cross and the United Nations.[154] It was not until 1994 that the NTP was

re-established on the basis of the DOTS strategy, relying on support from the WHO, World Food Programme, and international donors.[176]

The WHO implemented a two-tier program in Cambodia offering affordable but efficient health care, vastly improving the previous model of an unregulated private sector with poorly qualified healthcare staff and low-cost provision that lacked basic facilities such as running water.[154,175] The reformed Cambodian healthcare system was planned on the basis of epidemiological data to determine the relative burden in each region and supply resources accordingly.[154] This resulted in a planned supply of medications for TB in Cambodia, which when combined with an inpatient program and free meals for patients, resulted in markedly improved case detection rates.[154,176] Nevertheless, there was resistance among healthcare staff to change the conservative approach of central control, which was implemented through hospitals and centred on inpatient care, into a decentralised approach based around health centres for the treatment of infectious diseases such as TB with DOTS and microscopy provided at the community level.[154] Cambodia's success in establishing a new healthcare system to improve rates of TB suggests that, although TB incidence remains high at 345 cases per 100,000 population, there has been a consistent decrease since 2000.[177] This has been attributed to the funding sourced during the gradual handover to the Cambodian Ministry of Health, creating a self-sustaining NTP.[154]

In the Thai/Myanmar border region, funding gaps are closely associated with the lack of treatment availability, and TB control programs are encouraged to use resources wisely. Funding allocation for the treatment of HIV in Tak Province at the Thailand/Myanmar border is limited to one provider and does not allow HIV-positive, migrant patients to receive treatment owing to the long-term nature of the disease and high risks of migratory behaviour and subsequent treatment interruption.[178] The only exception to this rule applies to patients with TB/HIV coinfection, which is treated with donor funding, provided the quota for treating patients with TB has not been reached within the terms of the funding contract.[178] In this cross-border region, integrated HIV counselling, testing, and treatment within the TB control program is a measure that has been implemented to enhance TB/HIV case detection[178] and capitalise on treatment opportunities for co-infected patients.

Where funding is not associated with NGOs or private donors, government agencies develop their own initiatives to manage the health issues presented to them. In much of the developed world, testing and treatment is made available free of charge to patients. This is not the case in

the cross-border city of Baja, California, which borders Mexico. Although it is possible to conduct drug susceptibility testing, it is seldom performed because patients are unable to cover the costs.[179] In the four American states that comprise the Unites States side of the US–Mexico border region, only first-line TB drugs are funded by the US Government. Patients who are referred back to the Mexican health system for second-line treatment are then at the mercy of prohibitive controls. Second-line drugs are controlled by the Mexican National TB program, and the release of these drugs may take up to 6 months.[179] If US health facilities treat unauthorised Mexican visitors (those without documentation of citizenship or visas), the patients must pay upfront for TB treatment. Reimbursement is provided by the US Government only when emergency care is required.[180]

1.5.2.8 Cross Border Management/Control of Tuberculosis

(Appendix H: 3-5, 8, 14-15, 18, 22, 26, 29, 39, 42, 49, 52-53, 59-61, 66, 69, 73-75, 77, 90-91, 97, 105, 109, 116-117, 119-120, 128, 130, 138, 140-141, 154, 156, 164, 166, 191, 194, 198-199, 201-202, 206-207, 213, 215, 218, 223-224, 230, 234, 237, 245-246, 248, 250, 254-255, 259, 264, 274, 276, 282, 287, 289-293, 300, 324-327, 330-331, 336, 343, 347, 352; Appendix B: 376)

> In a globalized world characterized by profound disparities, migration is omnipresent. Tuberculosis is a paradigm of transmissible diseases that do not respect borders.
>
> - Matteelli et al. [181] *Travel Medicine and Infectious Disease*; 14,6: 588-590.

Cross-border TB transmission generally occur as a result of three main reasons, a) sub-populations fleeing conflict or persecution; b) patients with low socio-economic characteristics seeking health care or refuge in neighbouring countries with superior health care systems and c) migrant movement (including temporary) and subsequent importation of TB that is associated with the country of origin of the migrant.[40] Individuals partaking in cross-border movement purely for economic gain must also be taken into account; these include individuals from low-income populations who reside near a border and travel back and forth, mostly for economic reasons.[40] Host countries are required to implement interventions such as screening and ensure appropriate follow-up.[40,173]

While the management of migrant movement and immigration screening can be resource-intensive for host countries, most of the literature on the topic derived from high-income countries such as the USA and the United Kingdom. As the purpose of this scoping review was

to review the management of TB under challenging circumstances which may assist in identifying gaps in the literature and in shaping the operational response at the Australia / PNG international border, studies that related to migrant movement and immigration screening across international borders were excluded. The case of the Australian/PNG border will be examined more in detail in a subsequent narrative review.

1.5.2.8.1 TB management in the Tibet/India border region

Between 1994 and 1996, TB rates were very high – 835 cases per 100,000 population – among Tibetan refugees in India (Karnataka and Himachal Pradesh) who had been fleeing China over the previous 58 years.[182,183] In this population, greater mortality risk was significantly associated with advanced age and use of second-line therapy, which is required in cases of presumed MDR-TB or extensively drug-resistant TB (XDR-TB).[182] In a hospital-based study in the Tibetan Delek Hospital in Himachal Pradesh, TB was the reason for admission and cause of death for 23.2% and 30.1% of patients, respectively, between 1985 and 1992.[184] Relative success with TB control was achieved among the study population in Himachal Pradesh, where 80.1% of the 442 Tibetan patients infected with smear-positive TB were cured, and only 8.2% died.[184] Although this mortality rate is high by contemporary standards, these figures offered hope for treating TB among a refugee population from a high-incidence region in a high-incidence country. The success of TB control was attributed to the fact that the TB nurses and health workers lived close to the patients and belonged to the same community.[184]

In 2010, the incidence rate of TB in the Tibetan diaspora in India was 431 cases per 100,000 population; a marked improvement from the previous two decades.[59] Despite this improved rate, more recent research found that in 2010–2011, the rates of MDR-TB among new cases across five Tibetan settlements was very high (14.5%).[183] Of the MDR-TB isolates obtained from new cases, 28.6% were also resistant to ofloxacin, and 7.1% were resistant to kanamycin.[183] This rate of MDR-TB among new cases in the Tibetan diaspora in India well exceeds the comparative estimated global rate (3.7% of new cases), regional rate in Southeast Asia (2.1%), rate in China (5.7%), and rate in India (2.1%) for the 2011-2012 time period.[185] This finding may be attributed to the long-term effects of displacement and the high-stress circumstances experienced by refugees in the lead up to, and while escaping China, such as malnutrition, frostbite, hypothermia, and exhaustion, and exacerbated by overcrowding when first resettling as refugees in India.[183]

Figure 1.1.4 Tibetan Child Monks Review a Chest X-ray Image During Active TB Case Finding in Dehradun, India (Nurse Chemi Dolka, 2012).

1.5.2.8.2 TB management in the Thailand/Cambodia border region

Between 1974 and 1978, Pol Pot and the Khmer Rouge regime displaced the urban Kampuchean population, displaced families, destroyed health systems, killed all but 25 doctors, and systematically removed all traces of culture and formal education.[175] In 1979, Kampuchean refugees fled the Vietnamese invasion of Kampuchea and several years of the Khmer Rouge regime into evacuation camps in the comparatively safer Thailand.[186] In October 1979, the Government of Thailand agreed to open its border to displaced persons, and humanitarian aid efforts were provided by the United Nations and other NGOs.[187] By 1984, 21 refugee camps were established on the Kampuchean side of the border, with three camps on the Thai side,[186] for an estimated 600,000 refugees.[187]

Initially, diagnostics and treatment were not offered to patients with TB owing to uncertainties regarding the duration for which refuge would be required.[187] However, within weeks, laboratory support was made available, and all patients diagnosed with TB were transferred to

Khao-I-Dang on the Thai side of the border. Khao-I-Dang, and all other camps on both sides of the border, had an open-door policy, which resulted in excess patient movement, leading to high lost to follow-up rates. Eventually, the practice of confining the treatment of patients to a single camp was abandoned.[186] Thereafter, a TB control program managed by one TB program coordinator and staffed with locally recruited health workers with minimal training was established in each camp on the Kampuchean side of the border.[186]

It is likely that one of the greatest risks for patients with TB in terms of treatment loss to follow-up was the active military zone, which affected the residents of some camps on the Kampuchean side of the border. Between 1983 and 1985, 7 of the 21 Kampuchean border camps were destroyed by a Vietnamese offensive.[186] Eventually, in 1984, the violence on the Kampuchean side was so immense that the 240,000 residents of the 21 camps were moved into Thailand during a direct military attack.[186] Despite the upheaval, of the 376 patients who were under treatment at the time of the offensive, 371 were receiving treatment within a week of evacuation. Mastro and Coninx[186] highlight that the planned movement of patients with TB by truck greatly assisted at-risk patients who may have had difficulty walking. Unfortunately, secondary movement of refugees occurred when cooperation between NGO-run TB control programs and the Khmer administration faltered; consequently, 36 patients were lost to follow-up because they were moved to inaccessible locations by the Khmer administration.[186]

A persistent challenge to TB control among individuals in refugee camps is the high rate of persons lost to follow-up after TB treatment commencement. Unlike at other international borders, there was no option for cross-border collaboration, as there were no Khmer-run TB control activities during the 1970s, and the Cambodian NTP was not relaunched until 1995.[154] On the Thai side of the border, TB case finding and treatment was provided at the largest camp, Khao-I-Dang, by the Thai/Swiss Red Cross.[148] Between 1981 and 1984, among Kampuchean refugees living at Khao-I-Dang, TB was diagnosed in 629 individuals following initial presentation at one of four medical clinics placed throughout the camp and subsequent diagnosis at a TB clinic using microscopy and CXR.[148] To combat high loss to follow-up rates previously observed in other camps using 10- and 12-month regimens for Kampuchean refugees,[186] a 6-month anti-TB treatment regimen was implemented. Free daily DOTS was used for all patients to avoid black market trade,[188] and these efforts resulted in treatment completion of 73% of patients; only 2% of these did not show smear conversion by the end of

the treatment.[148] The remaining 27% comprised 15% who were transferred to other camps, 7% who had returned to Kampuchea, and 5% who had died during treatment.[148]

This relative success was attributed to using a shorter treatment regimen and ensuring that treatment was closely supervised to improve patient compliance.[148] With TB clinics located in each camp, the program was accessible to patients and used both Khmer personnel and administration support.[186] Finally, contextual issues were taken into account, whereby TB control program coordinators in each camp frequently provided updates to the medical coordinator of the primary health care coordination agency. These data were used by the United Nations Border Relief Operation (UNBRO) to establish and monitor the use of border-wide guidelines.[186] UNBRO also facilitated periodic meetings for camp TB control program coordinators where they were able to exchange ideas and experiences with each other.[186] Furthermore, TB control program coordinators were dedicated to maintaining TB control activities during times of unrest.[186]

While fragile states and conflict zones explain the bulk of cross-border movement and programmatic challenges, there are exceptions to the rule as evidenced by cross-border TB control program activities embedded in high-to-low–incident regions without the presence of violence. TB control programs across the borders between Finland and the Baltic States, between the United States of America (USA) and Mexico, and between Australia and Papua New Guinea are some examples.

1.5.2.8.3 TB management in the Finland/Baltic States border region

Much of Scandinavia is geographically protected from cross-border transmission risk; however, the same cannot be said for Finland, which shares a border with the Russian Federation – where the incidence rate is 66 TB cases per 100,000 population[189] – and a sea border with Estonia – where the incidence rate is 16 cases per 100,000 population.[190] Although Finland has not yet witnessed an increase in case numbers suggestive of cross-border transmission from the Baltic States, greater frequency of movement to and from both the Russian Federation and Estonia has been observed.[191] The close proximity and ease of transportation between Finland and the Baltic States heightens Finland's vulnerability to cross-border transmission of TB.[191] Unlike neighbouring Norway and Sweden, Finland does not have a cross-border screening program for any communicable diseases including TB, despite the perceived risk of cross-border transmission.[191]

1.5.2.8.4 TB management in the USA/Mexico border region

The USA/Mexico cross-border region spans 2,000 miles, involves 10 states (four situated in the US and six in Mexico), and extends 62.5 km in a north-to-south direction on both sides of the international line. This area encompasses a population of 11.4 million people living on the US side of the border,[192] where 1 million people cross the border each day.[180] The USA and Mexico have an incidence rate of 2.9 and 22 TB cases per 100,000 population, respectively.[193] TB transmitted from Mexican immigrants accounts for 75% of the cases reported in the four states bordering Mexico, and the case rate exceeds those in the interior regions of both countries.[180] Owing to the lack of a standard surveillance definition for binational cases, incidence rates are not available from border TB control programs; however, there are plans in place to rectify this gap for data analysis purposes.[194] The US TB policy and Mexican TB policy are derived from the Centers for Disease Control and Prevention and from the Ministry of Health, respectively.[192] Policy content is informed by each country's economic status and is geared toward high- or low-incidence settings.[192]

Most patients with TB in the border region use health services in both countries without notifying their country of origin or destination, and many TB cases must be managed in multiple health jurisdictions.[194] For unauthorised visitors to the USA, the threat of deportation impedes continuation of TB treatment.[194,195] Unauthorised visitors are not required to complete treatment prior to deportation; they are only required to be non-infectious.[196] Despite efforts at the state and federal levels, detainees are often repatriated before cross-border case management processes are implemented.[196] Inconsistency of treatment leading to interruption and loss to follow-up increases the risk of TB transmission and risk of development of MDR-TB.

Despite ongoing management of patients who might be diagnosed in one country and treated in the other, there is a limited number of health forums for staff on either side of the international line to discuss patient management strategies.[194] Various Memoranda of Understanding (MOUs) are in place to promote certain activities such as contact tracing and referrals; however, there are no bi-national guidelines or policies to support cross-border services.[194] There are also no shared documents that describe the legal framework and governance structures, which would potentially aid in fostering and strengthening bilateral cooperation.[197] In 2010, the US and Mexican governments implemented the US-Mexico Border Tuberculosis Consortium, which convenes annually. This is an opportunity for state

and government representatives to discuss issues pertaining to cross-border TB control, and jointly develop cross-border recommendations.[83]

To date, the US–Mexico Border Tuberculosis Consortium has helped to highlight inconsistencies across border programs and may assist with future cross-border collaboration. Regarding the delivery of DOTS, some programs delegate responsibility to a family member, whereas others require patients to attend the clinic; some clinics strive for 100% compliance, and others do not, and migration remains the greatest challenge at border clinics.[83] In terms of laboratory capacity and access, not all specimens in the US are sent for microscopy, culture, and drug susceptibility testing at the commencement of treatment because of distance from reference laboratories and limited staffing levels.[83] For specimens that are sent to the laboratory, the time required to receive the results varies, which strains the programs in regions with 20% of caseload showing drug resistance.[83] Drug sensitivity testing is not available in Mexico; thus, TB diagnostics are centred on microscopy and culture.[83]

County TB control programs at the US–Mexico border have implemented various tools and strategies to improve programmatic management of this highly mobile population. In San Diego, California, a TB binational card has been useful in managing cross-border patients. Studies are underway to improve drug adherence via the insertion of a microchip into pills, which once ingested sends a satellite signal to health providers to confirm the patient has taken the pill.[83] In Tijuana, Mexico, where the bulk of non-migratory patients reside, a dedicated staff member has been assigned to look after TB inmates.[83] Some programmatic interventions proposed under the US–Mexico Border Tuberculosis Consortium include the establishment of a cross-border electronic database to share patient information, development of standards and guidelines for patients with TB deported from the USA to Mexico, standardisation of MDR-TB/Diabetes and MDR-TB/HIV treatment regimens, and establishment of training and learning opportunities.[198]

In vulnerable populations under challenging circumstances, some key intervention strategies may be broadly applicable. The management of TB has historically been anchored in regimented and standardised treatment protocols. This largely involves a 6-month regimen for most TB patients. While effective for many, this universal approach is difficult for some patients to adhere to. Current TB regimens likely overtreat a large number of patients and might not be the most efficient or beneficial method for all patient populations.[199] The exploration of abbreviated TB treatments, such as 2 and 4-month regimens, could be particularly

advantageous.[199] While it is possible that this strategy could lead to relapse/retreatment in a small number of patients, the broader societal benefits could outweigh the associated risks.

1.6 Conclusion

This scoping review provides an overview of the challenges of managing TB under challenging circumstances, particularly in conflict and post-conflict regions, among refugee or nomadic populations, with coexisting diseases, following natural disasters, and at international borders. Specific thematic challenges include overcrowding, poor nutrition, financial constraints and health illiteracy and their impact on treatment delay, comorbidities, climate/geographical difficulties, damaged health infrastructure, limited human resources for health, insecurity, treatment interruptions, disrupted health services, uncertain allocation of financial resources, access, and cross-border health issues. Each theme is complex and is embedded within other social, medical, and political constructs. The End TB Strategy[10] describes four barriers to achieving the end of the TB epidemic, and each of these – weak health systems, underlying determinants of health (both social and physiological), lack of effective tools, and continuous unmet funding needs – has been explored within this scoping review.

The case studies discussed included examples of cohesive and well-planned strategies to reduce the spread of TB, despite complex or challenging contexts. For example, the successful TB control programs in India demonstrate the benefit of community support and locally selected outreach workers in conflict and post-conflict settings,[88] whereas the provision of food as an incentive was shown to be an important component in reducing TB rates in post-war Cambodia.[154] Integrating healthcare services into a basic package, built on partnerships with international organisations, and deploying funding streams effectively has resulted in good management of TB in Afghanistan.[42] Moreover, in remote areas, the most effective approaches may rely on the positioning of community health workers within the communities.[171] There has been relative success at treating high rates of TB among dynamic Kampuchean refugee populations escaping war in Thailand, reducing lost to follow-up rates over time owing to effective deployment of resources.[148,186]

Despite considerable lessons learned and demonstrated resilience of TB control program staff in the face of adversity, the effectiveness of one approach over another is dependent upon contextual anomalies. Whether TB control programs are operational during a crisis or experiencing sustained challenges, targeting vulnerable, underserved, and at-risk populations

requires good public health and economic policy with political commitment at the highest level.[10] Success of interventions or programmatic activities is often testament to the efforts of local staff, and they can be improved by good governance approaches. To ensure the greatest impact in complex settings, TB control program staff rely on decision makers and policy writers to be empowered to make necessary changes and allocate resources effectively.[10] Each challenging situation has specific risk factors and programmatic gaps; however, funding constraints, treatment interruptions, and a rise in MDR-TB are resounding themes globally. These considerations represent significant limitations on the ability of TB control programs to meet the challenging targets of the WHO to end TB, aiming to reduce the incidence of TB by 90% before 2035.[10]

1.7 References

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Figure 1.2 Torres Strait/Papua New Guinea International Border (Foster, 2014).

Chapter 1: Contextualising Tuberculosis
Part 2: Tuberculosis at the Torres Strait/ Papua New Guinea Border: A Narrative Review

1.8 Previous (Pre-COVID-19) Findings and Observations from the Region

Overarching Aim #1: Investigate cross-border TB disease epidemiology.

Overarching Aim #2: Identify opportunities for evidence-based enhanced policy and practice for the management of TB in the region (Translational Research).

Overarching Aim #3: Identify opportunities for strengthened cross-border communication and collaboration between Australia and PNG health services to better manage TB in the region.

Aims:

1. Describe the history of tuberculosis (TB) in Indigenous communities in Northern Australia.
2. Provide insight into the way TB is currently managed and discuss risk factors for transmission of TB in the Torres Strait / PNG border region.
3. Identify gaps in the literature to inform future research.

In this chapter I provide a background into the historical management of TB in Northern Australia and the effect of colonisation on TB in Indigenous communities. The themes characterising TB management in challenging circumstances that were identified in Chapter 1 (Table 1.1.1) provided a framework to examine TB management in the remote Torres Strait Islands of Australia in the complex Torres Strait / Papua New Guinea (PNG) borderland region.

I explore the history of TB control in Far North Queensland (FNQ), Australia. I also describe the social determinants of health relating to TB, clinical management of this disease and provide programmatic insight including an explanation of the stakeholders involved in cross-border health care. Outputs of this chapter includes the provision of the first detailed overview of managing TB in the Torres Strait / PNG international border region and the identification of

gaps in the literature which once addressed, may be used to enhance, and support policy and improve TB care in the region.

1.9 Contribution

My contribution to this chapter was as follows:

- I ran extensive literature searches in PubMed, Medline, and Scopus, and in grey literature for information and research on TB management in the Torres Strait / PNG international border region.
- I collected, cleaned, and collated other data to support this chapter.
- I attended workshops about writing literature reviews via the Cohort Doctoral Studies Program at James Cook University.
- I was the lead author of this chapter and shared drafts with my supervisory team.
- I took most of the photographs used in this chapter and have acknowledged those I did not take.
- I sought appropriate permissions to use some figures in this chapter.
- I analysed themes identified in Chapter 1, part 1 – TB and Global Challenges – Managing TB under challenging circumstances: a scoping review - Lessons from international settings, and selected those that were relevant to challenges in the management of TB described in this chapter.
- I then synthesised themes and information within this chapter to identify gaps in the literature and develop research questions for this thesis.
- It is important to note that some research questions were later developed in direct response to evidence derived from earlier studies in this thesis.

1.10 Impact of COVID-19 on the Research

In March, 2020, the international border between Australia and PNG closed due to the COVID-19 pandemic (Figure 1.2.1). At this time, data collection to support this research stopped as there were no longer any patients crossing the international border seeking healthcare in Australian health facilities. The Australian Government response was swift, and Australian Border Force and Australian Federal Police implemented strict border monitoring and control measures which included an increase in the presence of military and other personnel stationed on the northernmost islands of the Torres Strait and in surveillance vessels in the Torres Strait.

Figure 1.2.1 Torres Strait Treaty & Border Movements (Official Notice of the Australia / Papua New Guinea Border Closure Due to the COVID-19 pandemic). Source: Torres Strait Island Regional Council (March, 2020).[1]

According to the World Health Organization (WHO) Global TB Report 2021, the number of new TB cases reported in 2020 was 5.8 million whereas the actual number is more likely to be around 10 million.[2] Part of the impact of COVID-19 on global TB control is that millions of cases have gone undiagnosed and untreated. At the time of writing, the international border between the Torres Strait and the Treaty villages of the Western Province of PNG is still closed.

This narrative review was developed prior to COVID-19, between 2017 and 2019 and reflects the TB program in the region as it was at that time. Unless otherwise stated, the period of time that this narrative review covers, is pre-COVID-19. Any new information on the topic will be included in the data chapters.

1.11 Background

A structured scoping review was undertaken in part one of Chapter 1, to describe the range of literature available on managing TB under challenging circumstances from a global perspective. Themes identified in Chapter 1 (Table 1.1.2) will be explored herein, as they apply to TB control in Indigenous communities in remote Northern Australia and the Torres Strait / PNG border region. The history of TB in Aboriginal and/or and Torres Strait Islander peoples provides contextual background and allows for understanding of how the establishment of TB in remote areas has led to some of the challenges we see today.

The Global Plan to End TB provides strategies required to achieve the "90 (90) 90" targets which are to diagnose 90% of patients with TB, reach 90% of the most vulnerable populations and achieve treatment success for 90% of patients.[3] Indigenous peoples are recognised within the Global Plan to End TB as a vulnerable, underserved and at-risk population and the End TB Strategy provides three pillars to support adoption of the Global Plan.[3] Pillar one encompasses integrated, patient centred care and prevention. Pillar two calls for bold TB-related policies and supportive systems. Pillar three focusses on the intensification of TB research and innovation.[3] A lack of epidemiological data is characteristic of TB in Indigenous populations globally.[3] Underpinning this narrative review and indeed the whole thesis, is the recognition that Indigenous Australians are disproportionately affected by TB and require specific interventions that are culturally appropriate and cognisant of the challenges faced in remote Indigenous settings.[4] Efforts to reduce the burden of TB in the Australian Indigenous population will first require a comprehensive review on the management of TB in relevant settings, followed by an examination of the epidemiological profile of TB in Indigenous communities.

For the purpose of this narrative review, Northern Australia is defined as the Northern Territory and FNQ including the Torres Strait Islands. Less than five kilometres away at its closest point from the Australian Torres Strait Islands lies the Western Province of PNG. The WHO estimates that the incidence rate of TB in PNG is 432 cases per 100,000 population although due to limited surveillance, this is almost certainly an underestimation.[5] This international border in the Torres Strait / PNG region presents unique biosecurity risks and programmatic challenges for TB management.

TB control has changed over time in Australia and so too has the political commitment to ending TB in the Torres Strait / PNG border region. The Queensland TB Control Program was established in 1948.[6] The Cairns TB Control Unit was established in 1954 and ran remote outreach clinics to the Torres and Cape regions.[7] By 1959, a TB Sanitorium was established on Thursday Island (also known as TI) in the Torres Strait. Originally, two TB physicians managed TB in FNQ with one based in Cairns and the other on TI but by the late 1960s the physician in Cairns was responsible for the entire area.[8] In addition to providing TB services to residents of the Torres Strait and Cape York, the Cairns TB Control Unit provided a dedicated TB diagnostic and treatment service to PNG nationals from 2006 at the Australian / PNG border. However, the program closed in 2012 due to high rates of non-compliance with TB treatment regimens and the risk of amplification of multidrug-resistant TB (MDR-TB) in

the PNG population closest to the Australian border. By the end of 2012, Australian Aid (AusAID) had assisted with increasing the capacity of Daru General Hospital (DGH) TB Ward in PNG and PNG nationals presenting at Australian health facilities in the Torres Strait were being referred back to the PNG health system. The Cairns TB Control Unit continued to deliver monthly outreach services to residents of the Torres Strait and Cape York until the end of 2015. Despite some progress, logistical challenges hampered efforts to sustain an effective outreach service.[9] Rates of MDR-TB were increasing, and there was evidence of primary transmission of TB from PNG into the Torres Strait.[9,10] Cognisant of these risks, and based on the outcome of a gap analysis and wide community and stakeholder consultation, a funding proposal was written and submitted by the author of this thesis in 2015. The Queensland State Government funded the establishment of the Torres and Cape TB Control Unit, based on Thursday Island from January 1, 2016. This unit was Queensland's first TB Control Unit situated in an Indigenous community.

Missing from previously published literature, is a first-hand account, with programmatic insights, detailing how TB is managed in the Torres Strait / PNG border region. I am in the unique position as both PhD Candidate and Nursing Director of the TB Control Unit, based on Thursday Island. This narrative review aims to identify knowledge gaps and present findings and observations from the region including but not limited to the provision of a historical context; the challenges associated with TB control in remote Indigenous areas; the barriers and risk factors to effective TB control; the role of the TB nurse; stakeholder contributions, and the implementation of interventions and policy aimed to reduce the burden of TB in the region.

1.12 Introduction

Australia has one of the lowest incidence rates of TB in the world, which was reported as 5.5 cases per 100,000 population as at 2021.[11] Australia is considered a high income, low incidence country where the majority of TB cases are found in migrant populations. Another sub-population group considered at-risk for TB is Australian Indigenous communities.[12] Queensland and the Northern Territory, two of the three most Northern regions of Australia, are home to 37% of Australia's Indigenous population as at June 30, 2015.[13] In predominantly Indigenous communities in Northern Australia, TB transmission is often sustained within populations. In the Northern Territory, Indigenous Australians account for approximately 30% of all TB cases diagnosed[14] yet make up only 26.3% of the Northern Territory population.[15,16] In 2014 in the Northern Territory, the incidence of TB in Indigenous Australians was 28.4 per

100,000 population.[17] In the same year in the predominantly Indigenous Torres Strait Islands of FNQ, the incidence rate for TB was 218 per 100,000 population based on 2021 Census population data for the Torres Strait Islands.[18,19] According to the WHO, 40 cases per 100,000 population is deemed to be indicative of high incidence.[20] While rates of TB in Australian Indigenous populations have declined, it has been established that Indigenous populations are 6 times more likely to develop TB than non-Indigenous populations.[4,21] A study describing the burden of disease in Indigenous populations was conducted in 2011 and found that TB disproportionately affected more Australian Aboriginal and Torres Strait Islander populations when compared to non-Indigenous populations.[12]

1.13 TB in Indigenous Australians – from colonisation to today (2019; pre-COVID-19 pandemic)

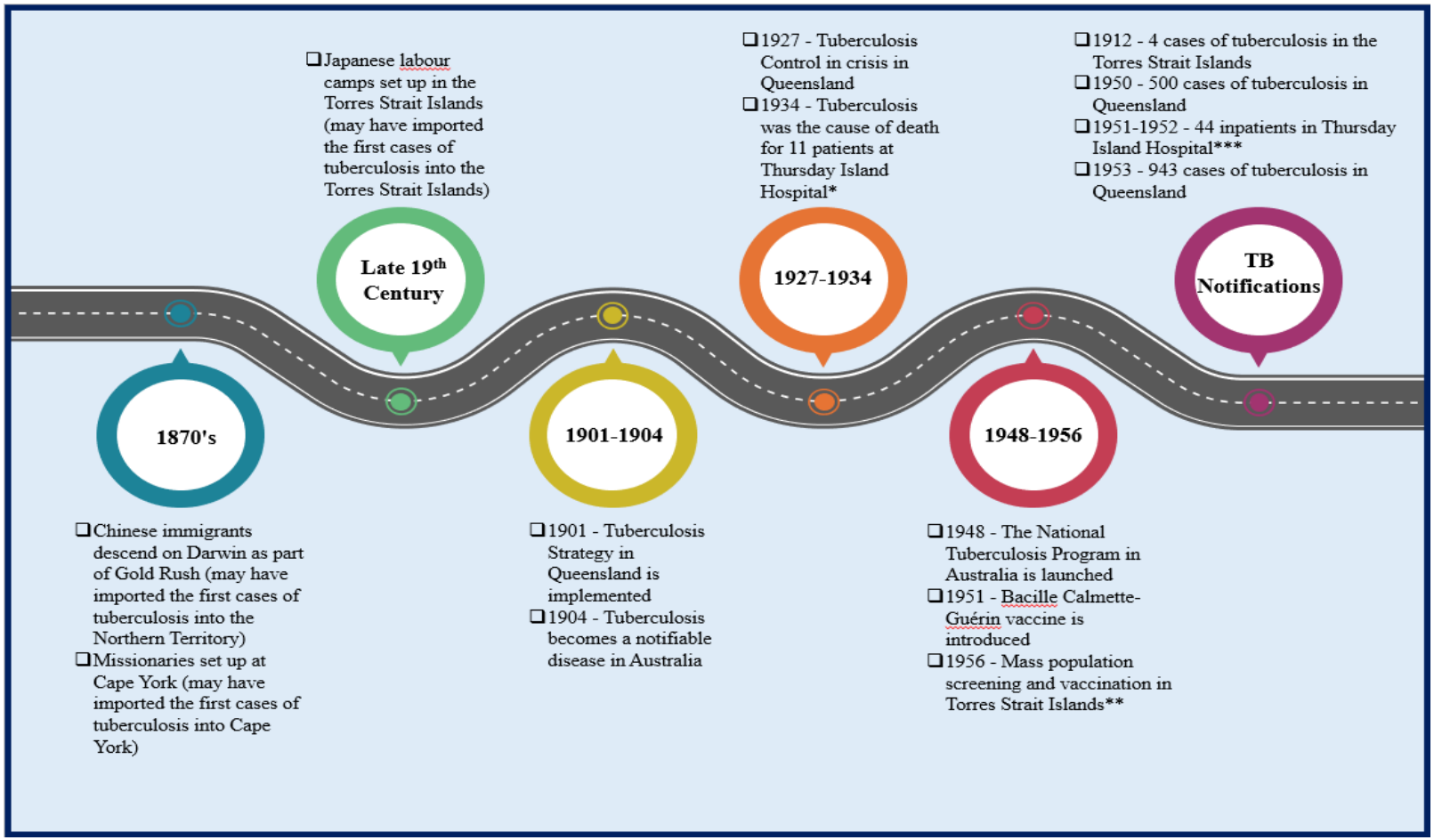
> One of the cardinal points in the epidemiology of tuberculosis is the terrible deadliness of the disease to newly exposed populations. We can hardly give adequate emphasis to the historical importance of this fact, tuberculosis, so virulent and fatal in fresh soil, has been a major ally of the urbanised European and American white man in the conquest of new territory, the demoralisation and destruction of aboriginal people.[22]
>
> - (Waksman, 1964)

Colonisation has had a profound effect on the health of Indigenous inhabitants of Australia, which is evidenced by high burdens of communicable and non-communicable diseases.[23] Based on paleopathological studies, there is no evidence of exposure to TB in mainland Aboriginals prior to the presence of Europeans.[24] Prior to European colonisation, Indigenous Australians were not without disease and depending on location, were affected by bacteria, protozoa, viruses and infections caused by arboviruses.[24] The presence of TB in Indigenous communities closely followed non-Indigenous occupation but the full impact wasn't apparent until after colonial subjugation.[8] TB was first recorded in Aboriginal peoples in the 1790s in the southern states, but it wasn't until the 20th century that it impacted the Indigenous peoples living in FNQ.[25] (Figure 1.2.2).

While Australia had long been protected from the plagues of Europe until the eighteenth century, isolation also played a role in protecting both mainland traditional inhabitants and those residing on offshore islands in the Northern Territory and FNQ. While there are reports that Chinese immigrants brought TB to some Indigenous communities in the Northern

Territory when gold was discovered south of Darwin,[25,26] European settlements had limited impact on these communities. The first European explorers of Northern Australia were inconsequential in regards to infectious diseases in these regions.[24] The bulk of newly introduced infectious diseases were found in colonial settlements closer to southern ports and it wasn't until nearly two centuries later that travellers and migrants brought diseases into Northern Australia.[24] From 1780 to 1850, approximately 50% of the European population had been affected by TB but could not be quarantined at colonial ports as symptoms were not always apparent.[24]

Where there was subjugation in North Queensland, there was TB. TB was described in Indigenous inhabitants in many of the North Queensland settlements. While a formal comparison has not been made in this thesis, historical record tends to document severe TB in Indigenous people, while at the same time describing TB as a chronic disease of low-grade activity in European settlers.[24] Potential reasons for this are: underlying health of the Indigenous population and genetic resilience of the European settlers, whose ancestors had centuries of previous exposure, compared with lack of previous exposure in Indigenous Australians. The overall prevalence of TB in non-Indigenous populations at the time was markedly higher than in the Indigenous population.[26] However, up until the mid-20th century, Indigenous peoples living outside of settlements and missions remained relatively unaffected by TB, in part owing to less crowded living conditions.[25]



Note. Incidence rates: a) 2010 – tuberculosis incidence rate 11 times higher in Indigenous population than in non-Indigenous population in Queensland#
b) 2014-2019 – tuberculosis incidence rate six times higher in Indigenous population than in non-Indigenous population in Queensland##
c) 1997 – tuberculosis incidence rate 35.9 per 100,000 population (Indigenous) compared to 2.3 cases per 100,000 population (non-Indigenous) in Far North Queensland^
d) 1984 – tuberculosis incidence rate 18.4 times higher in Indigenous population than non-Indigenous population in Queensland^
* (27); ** (28); *** (29); ^ (30); # (31); ## (32)

Figure 1.2.2 Timeline: TB in Indigenous communities in Northern Australia.

Due to a paucity of literature available, it is unknown when and by whom TB was first introduced into the Torres Strait Islands and Cape York; however, the literature contained some clues as to what the timeline may have been (Figure 1.2.2). A survey conducted in 1912 diagnosed four cases of TB in the Torres Strait Islands[6] but little insight is provided as to the transmission profile for these cases. Introduction to the Northern and Eastern islands of the Torres Strait most likely derived from the Territory of PNG where infection culminated in coastal communities and was directly related to the extent of contact that Melanesians had with Europeans.[33] Rates likely peaked in coastal villages and the Territory during World War II (1941-1945); when health services ceased to exist and TB patients were sent back to their villages.[33]

The introduction of TB in some of the Central islands of the Torres Strait and in Cape York communities, may have been as a result of Japanese labour settlements established in the late nineteenth century.[34] The first colonial settlement was established at the tip of Cape York in 1864, and the first missionaries arrived in the 1870s.[35] Both the Japanese and Europeans report an increase in TB related deaths in the late nineteenth century in the region. Strong kinship and trade connections throughout the region may have led to increased transmission of TB[34,35] where frequent inter-island travel occurred for trade and labour purposes, particularly to support the pearl diving industry.[33] Mass movement of people to central locations with good anchorage for pearl shelling led to overcrowded housing and changes in the traditional subsistence hunter-gatherer existence of local populations, which may have contributed to the burden of TB disease and population depletion.[35]

In 1901, Queensland first implemented various strategies to control TB including voluntary notification, sanatoria and hospitals to isolate and treat, and disinfection of these premises.[36] Despite this, notification rates in the Far North fluctuated, probably as a result of the lack of an adequate surveillance system. It wasn't until 1904 that TB became a notifiable disease.[37] Due to soldiers fighting in TB endemic countries, World War I saw mass casualties from TB, where some sanatoria in Queensland were reserved solely for ex-servicemen.[36] This had implications for the rest of the population afflicted by TB, as beds were in limited supply. Thus, strategies in place to control TB fell short, and in 1927, a Commonwealth report accused the state of Queensland of not responding to case notifications, only disinfecting premises post-mortem, and not following up on patients and their families post-discharge.[36] Detailed within the report were 67 recommendations, but these were not implemented due to the Great Depression of

1929 followed by World War II (1939-1945).[36] It was not until 1948 that there was a concerted effort at both state and federal levels to address the growing problem.

In 1948, the National Tuberculosis Campaign was successfully launched under the Tuberculosis Act,[30] but the Northern Territory was omitted from the scheme.[25] One strategy encouraged TB patients to refrain from paid employment by providing a generous stipend, thus reducing transmission risk.[30] This attempt to halt transmission had the added bonus of ensuring correct diagnosis and notification of cases – a requirement of the stipend – and garnered a more accurate picture of the TB burden with 500 notifications in 1950, and 943 by 1953 in Queensland.[36] However, while numbers were closer to being accurate in the non-Indigenous population, Indigenous Australians were unable to access this payment.[30]

In 1950, Queensland passed legislation to initiate free X-ray screening for TB.[38] Mobile vans visited both metropolitan and remote communities up until 1976. Impressive gains were made in reducing the incidence rate of TB in Australia from 28 per 100,000 to 5 per 100,000 population, however these gains were not observed in many Indigenous populations which were excluded during the campaign.[38] It wasn't until 1955 that free X-ray screening was available to Aboriginal people in the Northern Territory, and by 1959, X-ray screening was widely accessible and compulsory.[25,36] Most patients in the Northern Territory were treated as outpatients due to insufficient beds,[25] while an 80-bed sanatoria had been purpose-built on Thursday Island to cope with demand.[36] By this point, previous ineligibility for payment and screening had left many Indigenous peoples diseased.

Between 1950 and 1972, the average annual rate of TB among the Indigenous population of Queensland was 152 cases per 100,000 with extensive miliary and meningeal TB reported.[26] In 1951, Bacille Calmette–Guérin (BCG) immunisation campaigns in Queensland commenced, targeting both Indigenous and non-Indigenous populations.[39] The BCG vaccine first became available in the Northern Territory in 1952.[25] Despite regaining some control through BCG vaccination, active case finding surveys and the introduction of effective treatment meant notification rates remained high in Queensland with 739 in the 1950s, 629 in the 1960s and 237 in the 1970s.[6] It wasn't until 1978 that mean notification rates fell below 200 for the first time in Queensland.[6] In 1987, the incidence of TB in Indigenous Australians was 43.5 cases per 100,000 population compared to 3.8 in the non-Indigenous Australian population.[40] After adjusting for age, the rate in Indigenous Australians was 18.7 times that of non-Indigenous Australians.

By 1990, the incidence rate of TB in Indigenous Australians had increased to 20-50 times greater than in non-Indigenous Australian populations.[30] Furthermore, due to the poor quality of data, these estimates were likely to be an under-representation of the true burden of TB among Indigenous Australians.[30] Although the 1990's were a time when many TB epidemics increased, particularly due to concomitant HIV epidemics,[41] HIV was not a significant contributing factor in the region.[42,43] Between 1990-2000, TB incidence rates in Indigenous Northern Territorians remained 10-15 times higher than in non-Indigenous counterparts.[30] These rates remained high in 2014, at 13 times that of the non-Indigenous population of the Northern Territory and six times in Queensland.[32]

Originally, in 1954,[7] two chest physicians were appointed to look after the Far North – one in Cairns to focus on TB and other respiratory conditions, and one on Thursday Island to focus on TB in the Torres Strait Islands, Aboriginal communities and Christian missions on Cape York, and residents of the Papuan coast.[8] By the 1960s, new case numbers had fallen and the responsibility for TB control for Cairns, its Hinterland, Cape communities and the Torres Strait fell onto one physician located in Cairns.[8] Unlike in most other states and territories, TB services in Queensland were not disbanded in 1978.

The risk profile of TB transmission in Cairns at the time was via international visitors whereas PNG residents brought an influx of TB from the north into the islands and down to the Cape. The Thursday Island Sanatorium, with an 80 bed capacity,[44] closed decades ago but the numbers of active TB cases from PNG nationals in Thursday Island Hospital remains an ongoing issue.[8]

In FNQ, 57% of TB was diagnosed in Indigenous Australians between 1993-1997, where the incidence rate was 35.9 per 100,000 population per year compared with 2.3/100,000 in the non-Indigenous population.[30] Policy changes were implemented which included an increase in Directly Observed Therapy (DOT) with more aggressive and extended treatment for those who relapsed. These initiatives paid off, with only 24% of TB cases notified in Indigenous Australians from 1998-2002.[30]

1.13.1 Prevention

In the 1980s, in order to improve TB notification rates which were five times higher in Indigenous Australians than in non-Indigenous Australians, the BCG vaccine was more widely used in the Northern Territory than any other state in Australia.[45] The BCG vaccine also

provided prophylactic value for leprosy which was endemic at a low level at the time in this region.[45] Indigenous children in the Northern Territory received the BCG vaccine at birth and then again during the first year of high school in conjunction with routine tuberculin surveys.[45] However, in 1994 in the Northern Territory, rates among Indigenous Australians fell below the WHO prescribed 40 per 100,000 population threshold,[46] and tuberculin surveys in schools and routine BCGs for Indigenous children were ceased (V. Krause, personal communication, July 2019). Today the BCG vaccination program in the Northern Territory is targeted at children who will be travelling to high-risk countries for longer than 3 months with an incidence rate of over 40 cases per 100,000 population. In contrast, BCG vaccination remains core business for TB Control Programs in Queensland, with all Indigenous neonates and children aged less than five years eligible (in the absence of contraindications) to receive the vaccine.[47]

1.13.2 TB and the Social Determinants of Health

European settlement brought changes to the traditional way of life for Indigenous populations who were previously physically, socially and emotionally healthy.[26] Some scholars and physicians have raised questions in the past about genetic susceptibilities, and while this is a plausible line of enquiry, it is more likely that higher incidence and severity of disease in Indigenous Australians is attributed to social disadvantage.[26] TB in Indigenous communities emerged post-subjugation when their traditional way of life changed - overcrowded living conditions and malnutrition increased, which exacerbated the disease process.[26] Once a hunter-gatherer population, they were denounced and forced to enter a cash economy with people who did not speak their language. Unable to thrive in these circumstances, they started relying on handouts from those who had invaded their home. Persistence of TB continues today in Indigenous populations as many have not been able to overcome adversities and social inequalities related to poverty, overcrowding in substandard dwellings, and malnutrition.[26]

Social determinants of health such as poverty, unemployment, access issues to health care and a lack of education contribute to disease burden and are risk factors for TB in Indigenous populations.[48,49] In this regard, Indigenous Australian peoples have similar characteristics to residents of developing nations affected by TB.[21] Ongoing local transmission has been identified in Indigenous family groups in the Northern Territory[50] and this is in part due to congregate living, poor nutrition, poor hygiene practices and limited employment opportunities as well as a higher prevalence of risk factors such as diabetes, renal failure, smoking, and excessive alcohol consumption.[51]

Wide variability in TB rates between Indigenous and non-Indigenous Australians will continue to exist until such time that the social determinants of health are addressed in disadvantaged sub-population groups. In recognition of the need for equality among groups, 'Close the Gap' was a social awareness campaign launched in Australia in 2007 which aimed to address the health, education and life expectancy gaps between Indigenous and non-Indigenous populations.[52]

While TB has caused considerable mortality in family groups in FNQ, there is a lack of empirical investigation into the social determinants of the TB burden, and emerging evidence demonstrates a significant association between housing conditions and the burden of disease.[53,54]

1.13.3 Housing in Northern Australia

Three types of social housing are available to Indigenous Australians and these include public housing, community housing and state owned and managed housing.[55] Although wait times fell between 2013 and 2017, 17% of eligible Indigenous households waited for more than two years for housing during this time.[55] According to the Australian Institute of Health and Wellness, Indigenous Australians living in Remote and Very Remote areas in 2016, were 16 times more likely to reside in severely crowded housing than non-Indigenous Australians.[55] In 2016, 32% (n=4,087) of Indigenous households in the Northern Territory and 10.2% (n=7,593) in Queensland were considered overcrowded.[55] Aboriginal and Torres Strait Islander households are more likely to have multiple families living together than in the non-Indigenous population, with 3.2 persons per household compared with the national average of 2.6 persons per household.[56] Fluctuations of the number of habitants in Indigenous households can be linked to hosting visitors that are without stable accommodation, providing refuge for those experiencing social problems or violence, and opening up homes for cultural purposes such as church functions or funerals.[55] Overcrowded houses are often unstable and insecure environments which can lead to poor health of occupants, as pressure is applied to household facilities and budget.

Marked economical differences between the Australian and PNG border communities are obvious. Standards of living for Australian citizens living in the Torres Strait compared to PNG nationals living in villages of the Western Province close to the Australian border differ.[57] Australian citizens living in the Torres Strait have access to structurally sound housing,

electricity, clean water, free education, health care and financial assistance from the Australian Government. PNG nationals living in villages of the Western Province of PNG close to the Australian border live in makeshift huts made from vegetation such as dried palm fronds, corrugated iron or tarpaulin sheeting, have no access to electricity or sewerage systems and are dependent upon wells (which are not available in all villages) for clean water, which frequently run dry before the monsoon season rains can replenish them each year.[57,58]

In times of water crises, PNG nationals have been known to make their way to Australian islands to place containers and buckets underneath air conditioning units to collect the condensation to use as drinking water (Figure 1.2.3). Jobs are sparse and subsistence living is commonplace.[57] PNG nationals have also been known to take on cleaning or gardening roles within Australian households in the Torres Strait for hourly pay well beneath industrial award recommendations and Australia's minimum wage by law.[57] Despite the clear delineation of standards of living, crowded living conditions are a feature of both sub-populations[57] with as many as 25+ in some households on the Australian side of the border (personal observation, 2017).

A  B 

Figure 1.2.3 A garbage bin is placed under air conditioner units on Saibai Island collecting condensation to be used for drinking water for PNG nationals (Foster, 2017).

1.13.4 Access to Healthcare in Remote Tropical Communities

Managing TB in Indigenous communities has long been a challenge. In the 1970s fully supervised treatment was introduced, and in combination with community-based nursing, this strategy was a game-changer in southern parts of Australia.[45] The implementation of a similar approach has proven nearly impossible in the Northern Territory and some parts of FNQ due to long distances between nursing outposts and patients, particularly during the 'wet' season which can prevent access to health facilities.[45] Remote location is a predictor for high prevalence of TB disease in Indigenous communities and Northern Australian regions including the Torres Strait Islands, have long been affected by remoteness.[31]

For some residents of Northern Australia, the distance between outlying communities and health centres can vary considerably, with some patients needing to travel for many hours on dirt or corrugated roads or where access to community is limited to air or sea transport only. Consequently, patients may not be able to attend appointments, and staff may not always be able to provide outreach services.[45] For patients residing in extremely remote communities who require injectable medications or routine electrocardiograms (ECGs) to monitor side effects of the TB drug Bedaquiline,[59] TB physicians must weigh up whether admission to a tertiary hospital is required. For these patients, accessing these types of treatments and ancillary monitoring care may directly impact their ability to work, care for family and lead a normal life as well as add transport costs and promote feelings of isolation due to distance from community.[60]

In remote settings, desired levels of treatment supervision are not always feasible, which can impact on the compliance levels of patients, and may result in extended treatment, or complete abandonment of treatment. Transient populations are commonplace in remote communities. This lifestyle can affect access to health services and management of TB with frequent missed appointments and treatment compliance issues.[45] Excessive alcohol consumption can also lead to non-compliance as well as inhibit the therapeutic effect of TB medications.[45] Alcohol consumption can also interfere with patients remembering to take medications, and excessive consumption can prevent patients from successfully ingesting TB medications and attending their appointments. One way to mitigate these issues is for each patient to be part of a DOT program. DOT is where a health professional from the local Primary Health Centre (PHC) observes a TB patient taking each dose of TB medication to ensure compliance, monitor for side effects and keep patients motivated over many months of treatment.[61]

The role of the TB nurse in these tropical climates cannot be underestimated as concepts of disease and health in Indigenous populations need to be clearly communicated.[45] Tropical climate can affect the potency of medications and vaccines if not monitored and stored correctly.[45] TB nurses carrying vaccines and tuberculin to locations where health services do not exist may need to implement measures to manage the cold chain to ensure integrity of medications and vaccines during transport. They may require the use of cooler boxes packed with ice and/or secure electricity supply to keep vaccines and other medications cold overnight.[62] Conversely, when collecting samples from patients for diagnostic purposes, the high temperatures and distance from point of collection to laboratory can also be a challenge. For example, without prompt dispatch and maintenance of cold chain, sputum specimens are likely to become overgrown with other contaminating organisms jeopardising diagnosis.[63] Up to 2017 (year commencing research), **no studies in FNQ had been undertaken to determine the effect of appropriate collection, registration, labelling and packaging on the diagnostic yield of sputum specimens collected in the region.** This is addressed in Chapter 3.

1.14 Management of TB in Queensland: from 1950 to today (2019; pre-COVID-19 pandemic)

The Queensland TB Control Program is comprised of one metropolitan TB Control Unit in Brisbane (established in 1950) and in the five regional centres of Cairns (established in 1954); Townsville (established in 1955); Toowoomba (established in 1957), Rockhampton (established in 1958),[7] and Thursday Island (established in 2016) (see Figure 1.2.4). There is also a satellite service available from Mackay Hospital. Each TB Control Unit falls within a Hospital and Health Service (HHS) which are in and of themselves, statutory authorities.[64] The state-wide program is governed by the Communicable Diseases Branch (CDB) based in Herston, Brisbane under the auspice of the Queensland Department of Health. A Medical Director, Clinical Nurse Consultant, and a senior epidemiologist look after the state-wide TB portfolio. Prior to July 1, 2013, the state-wide TB program (Queensland TB Control Centre - QTBCC) was run out of Princess Alexandra Hospital in Brisbane.[7]

Figure 1.2.4 Queensland Health Hospital and Health Services.[65]

In September 2012, the Queensland Chief Health Officer advised the QTBCC that TB services would be managed within HHSs and governed by the 'System Manager' which would be the CDB within the Queensland Department of Health.[7] This directive to disband the state-wide TB program QTBCC led to protests that reached the Australian Parliament.[7] Negotiations resulted in clinical TB services for south-east Queensland being moved under the Infectious Diseases Unit of Metro South HHS, whereby 27.3 full-time equivalent staff (FTE) of 40FTE remained.[7]

As the System Manager, responsibilities of the CDB include management of the Notifiable Conditions System and vaccination records, responding to issues of state-wide significance including information sharing about stock issues, briefing the Chief Health Officer / Director General on important developments, provision and helpdesk support for a TB information system, writing policies and directives, and chairing the Queensland TB Advisory Group, later changing its name to the TB Expert Advisory Group (TEAG), where complex TB cases and issues are discussed monthly. All TB Control Units in Queensland have teams of nurses and onsite TB physicians with the exception of the Torres and Cape TB Control Unit on Thursday Island for which the TB physicians are based in Cairns and Townsville. TB Control Programs are still relevant in Australia due to long lasting periods between infection and manifestation of active TB disease in exposed Indigenous populations and in migrants and refugees.[45]

1.14.1 Laboratory Support in Queensland

Queensland HHSs send sputum specimens, histological samples and blood for Interferon Gamma Release Assay (IGRA) to Queensland Pathology laboratories primarily located on hospital campuses in the first instance. Sputum and histological samples are checked for correct identity, registered, and then re-packaged for transport to the Queensland Mycobacterium Reference Laboratory (QMRL).

The QMRL is the central reference point for the determination of mycobacteria testing including culture, drug sensitivity testing and genetic typing[5] (Figure 1.2.5). QMRL is based in Brisbane at the Royal Brisbane Hospital, and all positive results are communicated directly to TB Control Unit. TB Unit staff also have access to Queensland Health's laboratory information and results system AUSLAB for the purpose of monitoring specimens and managing patients.

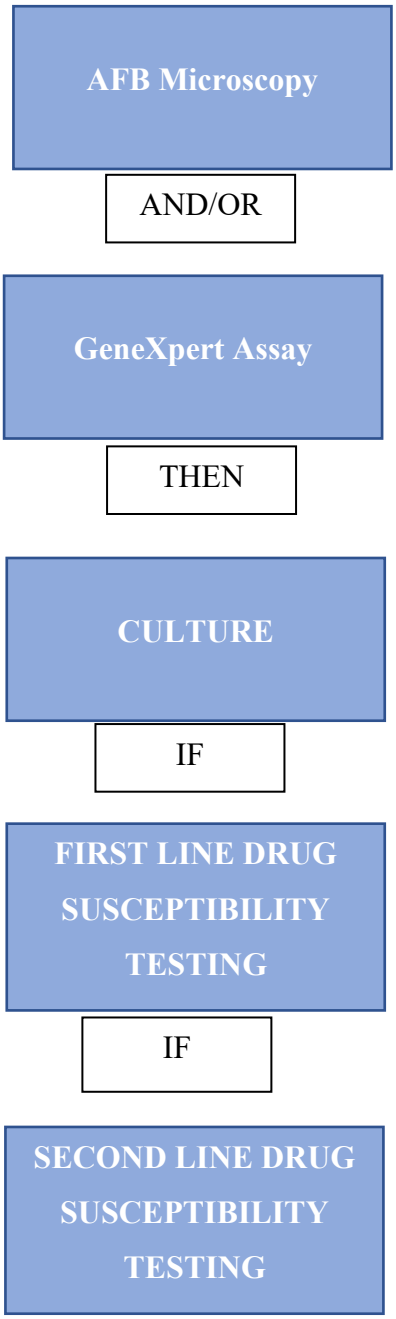


Figure 1.2.5 Laboratory Analyses – Standard Diagnostic Pathway.

1.14.2 The role of the Queensland TB Nurse

The role of the TB nurse requires specialised knowledge on the whole continuum of TB care. The TB nurse needs to understand transmission risk both from a biomedical perspective as well as one embedded within the social determinants of health. The TB nurse's role is underpinned by knowledge of the pathophysiology of TB including the clinical manifestations of primary, secondary and dormant phases, and must also be proficient at clinical assessment and reading,

understanding, and interpreting various laboratory-based and point of care results. TB nurses are responsible for activities related to TB prevention through early detection of disease, screening, surveillance and by working collaboratively with other nursing specialties such as Infection Prevention and Control to reduce microbial contamination within healthcare facilities, or with maternal and child health to ensure adequate vaccination coverage. The TB nurse is also responsible for TB case management and supporting patients through lengthy treatment regimens that require monitoring of adverse effects and arranging baseline, routine and ad hoc blood and other specimen collection for evaluation.

1.14.2.1 TB Nursing: Contact Tracing & Screening

A third of the world's population is infected with MTB, and it is the responsibility of the Queensland TB nurse to identify individuals with immunologic evidence of TB infection in high-risk patients such as those who have been exposed to a known case of TB and in those who are employed in high-risk zones.[66] The tuberculin skin test (TST) involves intradermal injection of mycobacterial purified protein derivative.[67] When interpreting results, allowances must be made for prior BCG vaccination.[67] A positive TST result is suggestive of Latent TB Infection (LTBI) however its use in the tropics may be complicated by non-tuberculous mycobacteria (NTM) found in the environment.[66]

IGRAs, while benefiting from using TB-specific antigens, thereby reducing false positives related to cross-reactivity with NTMs and the BCG vaccine, may be used.[66,68] Relying exclusively on TST positivity before administering an IGRA would undermine the overall detection rate of TB infection, however, double testing is recommended in some countries to address treatment hesitancy after a significant TST result.[69] Both TST and IGRAs have limitations in sensitivity and don't always align perfectly in their results.[70] There exist cases where individuals with a genuine TB infection might test positive on TST but not on IGRA and vice versa.[70] While IGRAs offer advantages in specificity, they aren't flawless.

IGRAs can cost patients up to $AUD100 if sourced outside of the public health system and require reliable laboratory support.[66] Nevertheless, the TST remains the preferred method of identifying TB infection in Queensland.[66] If cases of LTBI are diagnosed and treated within two years post-exposure, the risk of reactivation and potential community transmission is greatly reduced.[66] Active TB disease must always be ruled out prior to commencing patients on treatment for LTBI.[66]

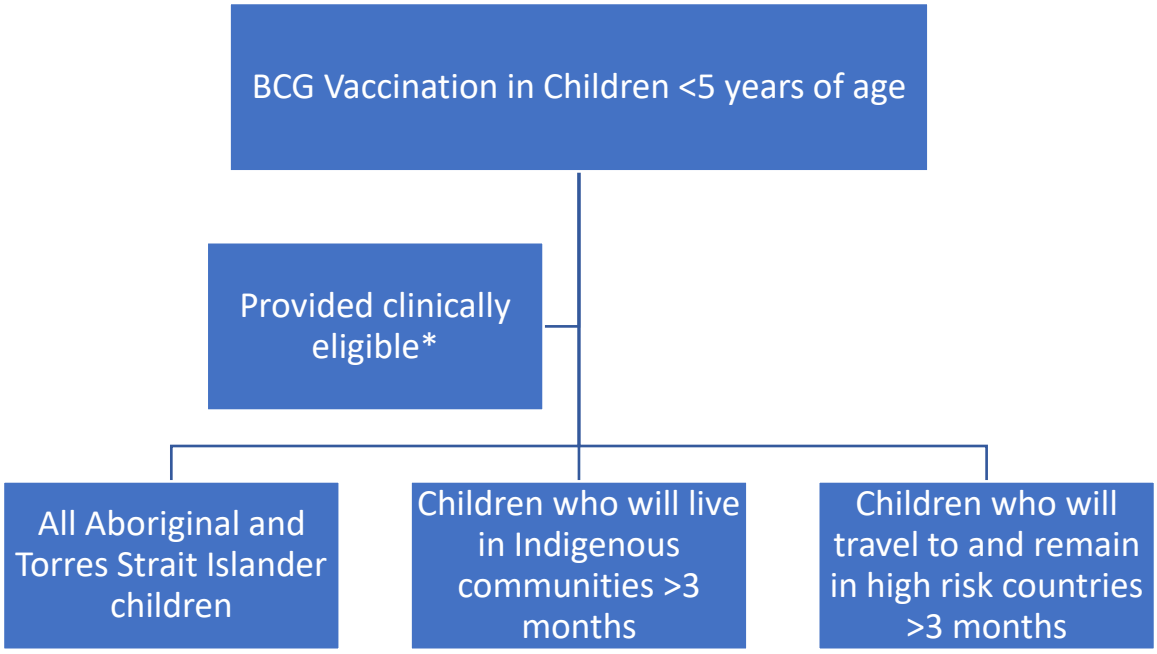
Konstantinos[71] outlines the TB testing protocol for Queensland which identifies residents of Aboriginal and Torres Strait Islander communities as high-risk for TB infection due to increased risk of exposure. This is particularly evident in the Torres Strait Islander population, given their proximity to TB endemic PNG and the likelihood of repeated exposure. As with other TB programs provided to Indigenous communities, TB nurse-led contact tracing and screening activities in the Torres Strait are aided by close-knit social structures and the assistance of Indigenous Health Workers based in each community.[72]

The Queensland TB Program mostly functions with minimal use of IGRAs to detect infection, however, this approach is slowly changing in FNQ to combat repeated TB exposure in some sub-population groups. The TST or IGRA are offered to new health professional recruits or existing staff working in high-risk areas. The decision of which test to use is based on risk profile, past medical history,[69] or availability of nurses with relevant skills. The location of the health professional also features in the decision-making process, where those servicing the most remote locations, are often offered IGRAs. Regardless of TST or IGRA results, the BCG vaccine is generally not offered to health professionals in FNQ and its protective value is far more beneficial in the paediatric population.[47]

1.14.2.2 TB Nursing: BCG Vaccination

In Queensland, only TB nurses can train and accredit in the intradermal technique required for the administration of both tuberculin and BCG vaccine, provided the nurse-led trainer is an experienced TB clinician.[73,74] Senior nurses in TB Control Units must arrange to re-accredit each other and the frequency with which reaccreditation is required is at the discretion of HHSs.[75] Frequent staff turnover in remote areas can quickly lead to an unskilled TB nursing workforce requiring considerable investment to upskill.[76] In 2019, the cost to train a new TB nurse based on TI in TST and BCG administration was in excess of $35,000. In 2017, with no in-house TB nurses accredited for 12 months, and no other larger TB Control Unit in Queensland actively providing a BCG program, assistance via secondment was sought from a nurse within the Townsville TB Control Unit. As residents requiring TST and BCG were widely dispersed across the Torres Strait and Cape communities, extensive travel via boat, helicopter and fixed wing aircraft was required for the new TB nurse to meet the minimum requirement of 20 successful attempts per TST and BCG (personal observation, 2017).

In February 2021, two TB Control Units in Far/North Queensland (the Torres and Cape TB Control Unit and Townsville TB Control Unit) commenced a Direct BCG program whereby TST was not required prior to BCG vaccination in most instances. Up until February 2021, BCG administration required a TST to be administered prior to vaccinating children over the age of 6 months. TSTs had to be administered on day one, and then read / interpreted 48-72 hours later. Eligible children younger than 6 months of age could receive the BCG vaccine without an initial TST. The majority of children in Queensland do not require BCG vaccination,[77] however, this is not the case in the Torres Strait and Cape York regions of FNQ where approximately 95% of children are eligible (excluding contraindications); Figure 1.2.6. It should be noted that BCG supply interruptions have led to adhoc administration since 2012.[78]



*Contraindications for BCG vaccination includes children with weight <2500g, positive TST result, severe malnutrition, impaired immunity, recipient of immunosuppressive treatment and recipient of another live attenuated vaccine (measles, mumps, rubella; yellow fever) within past month.[47]

Figure 1.2.6 BCG vaccination eligibility in the Torres and Cape Hospital and Health Service.

1.14.2.3 TB Nursing: Education & Community Consultation

TB nurses rely heavily on many stakeholders to deliver TB services to enhance and improve care, reduce inequalities, overcome geographical boundaries and strive for service equity.[79] This is particularly true in remote and regional settings where local TB units must achieve standards of care and rapidly respond to incidences of public health significance. To effectively

provide uninterrupted support to at-risk communities, it is the responsibility of the TB nurse to deliver tools and strategies to local communities to enhance their knowledge of TB.[79]

While all patients with TB are assigned a case manager from within TB Control Units in Queensland, local models of care can provide enhanced support for patients to ensure that they can access a level of care corresponding to their needs. This is achieved by TB nurses conducting regular education sessions[79] for both hospital and PHC staff which includes case studies, benchmarking against national standards and in-services. With support from TB nurses, hospital and PHC clinicians play an important role in identifying at-risk or symptomatic individuals, contact tracing, delivery of DOT, and radiological and microbiological investigations.[79]

Although there have been no studies in the region to determine the impact of good or poor-quality specimens on diagnostic yield (this is addressed in Chapter 3), efforts to improve the quality of sputum specimens collected have been undertaken since 2016. This has included procedure development and basic training for health service clinicians undertaking sputum induction as well as distribution of posters to assist clinicians to provide instructions for symptomatic patients to voluntarily expectorate.

The Queensland TB Program uses a passive case detection approach, where patients self-present to a PHC with symptoms and if TB is diagnosed, targeted screening of close contacts and treatment for the index case follows. At the other end of the case finding spectrum is active TB case finding, which is resource intensive, requires sufficient health infrastructure and human resources[80] and is generally not activated in Queensland. In both scenarios, diagnosis is delayed in the Torres Strait due to an absence of advanced diagnostic technology. **No research has been undertaken to date in the Torres Strait / PNG border region that examines the role of TB knowledge with the passive case detection model used in the Torres Strait and how it impacts the identification of symptomatic patients, diagnosing and the commencement on effective treatment for symptomatic patients.** This is addressed in Chapter 4.

TB nurse-led counselling, education and local support at a grassroots level is an integral part of the management of all persons with TB in the remote communities.[79] Persons with infectious TB must receive culturally and linguistically appropriate counselling and education to ensure that they understand the public health significance of their diagnosis and the importance of

complying with treatment and isolation.[75] The active presence of a local TB service in the community, which includes Indigenous representation, aids building community confidence in the health system.[54,81]

Surveillance data in Queensland is reported based on location and includes Indigenous status but there are few publications which focus on TB in Torres Strait Islander peoples alone. The concept of health care is in itself perceived differently between Aboriginal and Torres Strait Islanders, and while aspects of social and environmental factors on health status are found in both sub-populations,[82] the risk of TB infection and perceived threat of disease differs. For this reason, community consultation and participation in the development of TB control strategies must be considered an important part of ending TB in the region.

1.14.2.4 TB Nursing: Case Management

While case managers are not directly responsible for prescribing or administering TB medications, TB nurses as case managers of patients with TB are the central point of contact for patients with adverse events or complications from TB treatment regimens and are responsible for collaborating with pharmacies to arrange the safe delivery of TB medications to patients. TB nurses coordinate all follow-up care; monitoring and sharing results; arranging chest X-rays (CXR) for TB patients or those on lengthy CXR surveillance programs; blood collection; performing ECGs; taking sets of observations; booking appointments for patients to see TB physicians, and being the focal point of contact and the support person for patients and their families. With specialised knowledge, TB nurses provide education about TB for patients, families, community, health professionals and the wider public.

Like all health professionals, TB nurses must adhere to legislative requirements for notifiable disease notifications including reporting treatment outcomes and identifying risk factors. A significant part of TB nurses' workload is dedicated to document management and administrative procedures relating to patient care that require robust and supportive systems and software which are not always available in remote settings.

1.14.2.5 TB Nursing: Adverse Event Management

TB nurses must be receptive to the possibility of adverse events occurring at any time in three separate TB care portfolios:

1. Patients on treatment for LTBI
2. Patients on treatment for Active TB disease
3. Patients who have received the BCG vaccine

Managing milder side effects of TB medication used to treat both Latent and Active TB disease such as nausea, vomiting or upset stomach can often easily be rectified by changing the time of day the medication is ingested, after discussion and collaboration with a TB physician. Rifampicin is known to render some forms of contraception ineffective so barrier methods of contraception may be indicated while patients are on treatment.[83]

There are however, other, more severe adverse effects of TB medications that are known to lead to ocular toxicity as evidenced by changes in a patient's visual acuity; liver impairment as evidenced by deranged blood results and hearing loss to name a few.[84] The TB nurse as a DOT supervisor is responsible for monitoring for treatment adherence, the presence of side effects and arranging any follow-up tests. This assists with early recognition of any of these severe adverse effects of TB medication and should prompt immediate notification to a TB physician.

The requirements of nurses in adverse event management post-BCG vaccination are well documented.[85] If anaphylaxis occurs, this requires immediate emergency medical management and TB nurses must always carry an anaphylaxis kit when undertaking BCG clinics.[85] Any serious or unexpected adverse event following immunisation (AEFI) requires TB nurses to notify a TB physician and complete an AEFI report form which is submitted to the Queensland Department of Health for recording on a state register.[85] Appropriate follow-up of the patient is also required.

Rare adverse reactions post-BCG may include persistent or localised lymphadenopathy, severe erythema at the injection site with tenderness or abscess formation.[86] Disseminated disease may also occur but this is considered to be an extremely rare adverse reaction.[86,87] Each of these reactions typically occurs due to inadequate intradermal injection technique or accidental subcutaneous injection.[87]

1.14.2.6 TB Nursing: Managing presumed TB cases

TB nurses work closely with Infection Prevention and Control nurses to provide advice to multidisciplinary teams and PHCs regarding isolation requirements for patients with suspected or confirmed pulmonary TB.[88] Under the direction of TB physicians, TB nurses arrange for

CXRs and specimen collection from patients under investigation for TB. On some occasions, other specialist services are required and the TB nurse helps to support inter-hospital transfers and liaises with receiving TB nursing teams. It is also important for TB nurses to provide comfort, advice and support to patients with presumed TB, as the wait for results, particularly in remote regions, can take many days.

1.15 Management of TB in FNQ: (pre-COVID-19 pandemic)

There are three HHSs providing health care in North and FNQ and their TB Control Units are located in Cairns, Townsville and Thursday Island.[78] TB Control Units in both Cairns and Townsville are located within tertiary hospitals whereas the Torres and Cape TB Control Unit is a structured outpatient service which also provides inpatient support. Cairns and Townsville serve their respective metropolitan areas as well as more remote settings such as Hughenden and Palm Island.[89] Further, they share responsibility for communities located in North West and Central West Queensland. Based on Thursday Island, the Torres and Cape TB Control Unit is responsible for servicing all Torres Strait Islands and Northern Peninsula Area, as well as Cape York communities surrounding the regional hubs of Weipa and Cooktown (Figure 1.2.7).

The Torres and Cape TB Control Unit commenced operations in January 2016 and at that time was comprised of a full-time Nursing Director, Clinical Nurse Consultant, Indigenous Health Worker and Administration Officer based on Thursday Island, and a part-time TB Specialist based in Townsville. During the first year of operation, a further 0.2FTE TB Specialist based in Cairns was added to the team. Each TB Specialist is rostered on a monthly rotation and TB Specialist Clinics are held once every three months. Both specialists travel to Thursday Island and relevant communities during those visits to consult with patients with Latent and Active TB. Opportunistic education is also provided to health facility staff during these visits, and to patients and families as required. In 2019, a marked increase in TB-related activities in the Torres and Cape HHS led to the appointment of a full-time TB Clinical Nurse based on Thursday Island and an Indigenous Health Worker based on Saibai Island.

The Torres and Cape HHS services a population of over 25,000 people, of which 63.7% identify as Indigenous.[90] In 2016, the population of the Torres Strait Islands was 6,487 where approximately 2000 people transiently reside on Thursday Island.[91] In the Torres Strait Islands and Northern Peninsula Area, 80% of individuals identify as Torres Strait Islander.[91] The northern boundary is adjacent to PNG. In the Torres Strait, Thursday Island is the

administrative centre and the only island with a hospital. The Torres Strait is comprised of approximately 274 islands, of which 17 are inhabited.[91] As at 2016, population numbers across the outer islands were between 69 (Stephen Island) and 697 (Badu Island).[91]

The 17 inhabited islands in the Torres Strait (Figures 1.2.7 and 1.2.13) are divided into 5 clusters – Saibai, Boigu and Dauan in the Top Western Cluster closest to PNG; Badu, Mabuiag and Moa in the Near Western Cluster; Yam, Warraber, Coconut and Masig in the Central Cluster; Murray, Darnley and Stephen in the Eastern Cluster, and Horn, Hammond, Prince of Wales and Thursday in the Thursday Island group.[92] The distance from the most northern island of Boigu in the Top Western Cluster to the main administrative hub, located on Thursday Island, is 145 kilometres and access between these islands is by a 45-minute fixed wing flight from Horn Island which is a 10-minute boat ride from Thursday Island. Thursday Island is 802 kilometres from its nearest regional centre, Cairns (Figure 1.2.7).

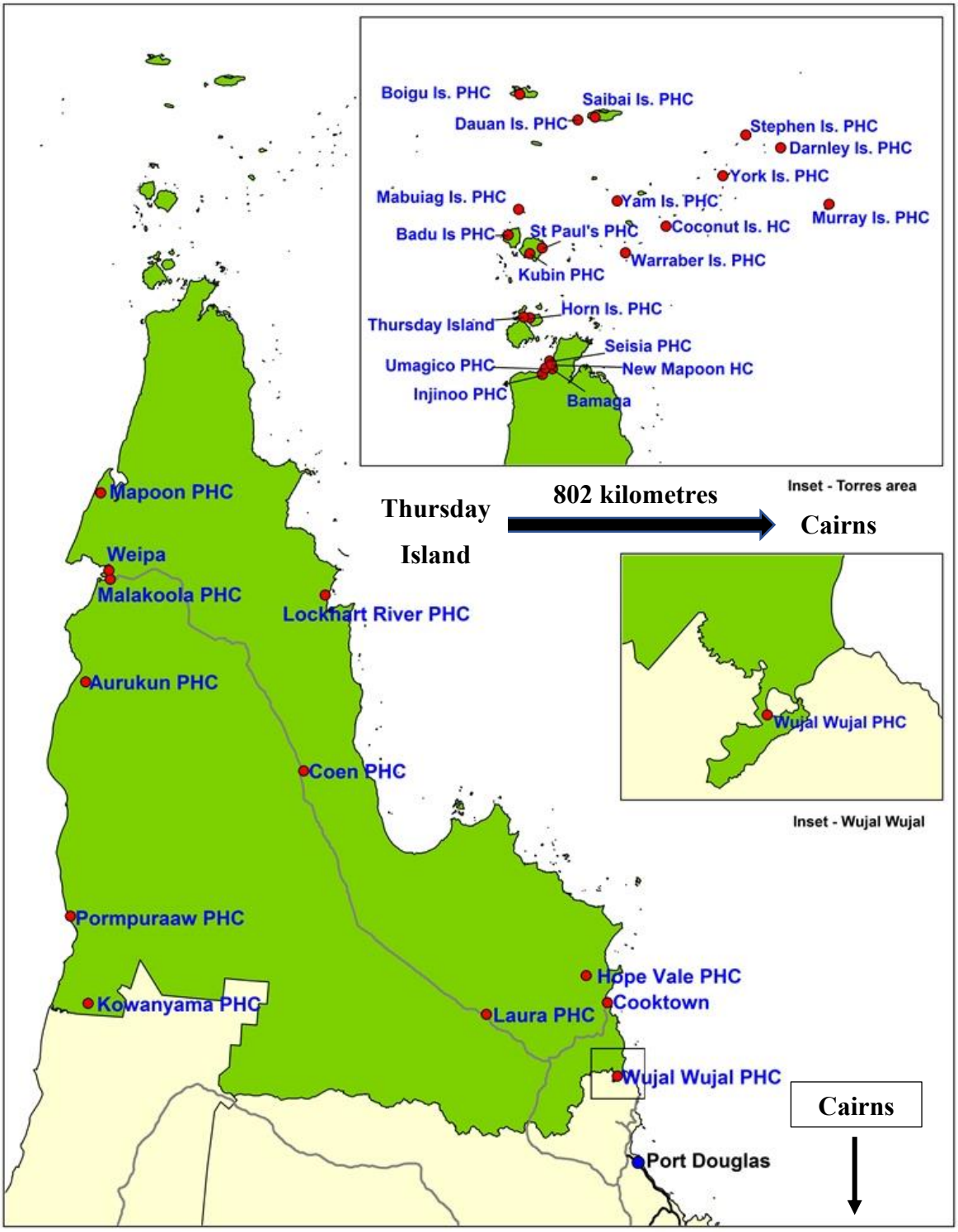


Figure 1.2.7 Torres and Cape Hospital and Health Service jurisdiction.[90]

Most islands are serviced at least once a week by a commercial airline, and have a supermarket, local Council office and PHC. Hammond and Prince of Wales Islands do not have commercial transport access or a PHC. Moa Island has two communities, St Pauls and Kubin; each has a PHC. The majority of PHC are one-nurse posts with the exception of Thursday, Horn, Saibai, Boigu and Badu Islands (see Figure 1.2.7 for location of the Torres Strait Islands). Most islands also have community police presence and a primary school. A weekly barge delivers goods to each island.

Aeromedical evacuation support is provided by Queensland Health (including Queensland Ambulance Service and the Aeromedical Retrieval and Disaster Management Branch) and the Royal Flying Doctors Service (more detail is available in Chapter 5). Each island is visited at least once a month by a doctor and if a patient is required to attend Thursday Island Hospital (Figure 1.2.8), no out of pocket expenses including flights, accommodation or inpatient services are incurred by both PNG nationals and residents of Australia. Only Saibai and Boigu islands have X-ray facilities, with staff trained and accredited to use them. Appendices J9 and J10[88,93] describe how presumed pulmonary TB is managed for residents in the Torres Strait and Cape York communities.

Figure 1.2.8 Thursday Island aerial view (Foster, 2019).

Figure 1.2.9 Boigu Island aerial view (Foster, 2019).

Accessing communities in Queensland's Cape York also presents logistical challenges for TB program staff. With the Torres and Cape TB Control Unit based on Thursday Island, staff must generally travel via Cairns to reach Weipa or Cooktown. Travel to other communities in the Cape is then either undertaken by 4WDs or by small commercial or charter flights. This comes at significant expense to Queensland Health with the added effect of placing TB Control Unit staff at risk of fatigue and in a position where they are time-poor to complete clinical duties. Leading BCG clinics in an ideal setting would involve administering the TST to children >6 months of age on day one, and returning to read results and administer the BCG vaccine to eligible children 72 hours later.[73] This was not possible for the Torres and Cape TB Control Unit nurses servicing Cape communities as Mondays and Fridays are reserved for travel, leaving Tuesday as the TST day and Thursday as the day to read the TST results and administer the BCG vaccine. A minimum gap of 48 hours must take place between TST and BCG.[73] From a cultural perspective, this can be very challenging, and does not adequately support community or PHC engagement.

As the TB Control Unit is not based in Cape York, the community may not be familiar with the staff or remit of the service, and may actively avoid staff due to fear and stigma of TB. To help with this, staff do not wear uniforms identifying their involvement with the TB Control Unit. Patients diagnosed with TB in the Torres and Cape are provided education about their diagnosis, treatment and follow-up required. Considerations allowing patients to determine

which family members should be invited to patient appointments and education sessions is always at the forefront of clinicians' minds in the Torres Strait. Advice and insight from Indigenous Health Workers enables non-Indigenous clinicians to also identify appropriate family members to help support patients, however the Torres Strait TB Control Unit is the only TB Control Unit in Queensland that employs an Indigenous Health Worker. Many households in the Torres Strait are multigenerational and patients often have strong connection to family.[12] Part of cultural norms and responsibilities attributed to family and kinship include support passed from generation to generation when a member of the household experiences stress or illness.[94]

Providing community education is within the TB Control Unit service portfolio, but a lack of staff and increasing burden of disease control activities has hampered preventative activities. It is respectful practice to spend time in community to establish relationships with both health centre staff and community members. With tight schedules, patients are provided designated appointment times, however the appointment method is usually not ideal in many of these communities. Trust becomes difficult to establish if no time is permitted for 'yarning'. A lack of an established trustworthy relationship between health staff and community members may result in few people presenting at health care centres. Further, it is imperative that TB clinicians have the support and time of locally-based Indigenous Health Workers which can place a strain on PHCs given the vital role that Indigenous Health Workers play in the day to day running of PHCs. The Torres and Cape TB Control Unit realised shortly after its establishment that rushing clinics in the Cape would not enable the delivery of safe, supportive and responsive health care or trustworthy relationships with local communities, and would lead to many children being missed and not receiving their BCG vaccination. It is for this reason that TB Control Unit staff (from 2017) either travel on weekends (and receive time off in lieu) or a flight is chartered directly from Horn Island to the target community. However, despite this community-centred approach to health care and high levels of planning and complex logistics, the TB management program may still be hampered in the event of sad news or sorry business (death in the community) in Indigenous communities, as staff are then unable to go to these remote communities to deliver their TB service.

The burden of TB is higher in the Torres Strait and there are more patients on DOT for LTBI and Active TB disease than on mainland Australia. All TB patients in the Torres Strait, whether for LTBI and Active TB disease, are eligible for DOT in the Torres and Cape HHS. As well as

being recipients of DOT, patients with LTBI receive a home visit by a TB case manager nurse once every three months, and those with active TB disease receive monthly visits. This, coupled with representation of TB Control Unit staff at staff education days, has led to the establishment of solid relationships between TB clinicians and the Torres Strait community.

Since 2015, TB nurses in the Torres and Cape TB Control Unit have regularly partnered with the Torres Strait Island Regional Council and the Department of Foreign Affairs and Trade (DFAT) to deliver community-based education on the signs and symptoms of TB, as well as shared information on how to protect themselves and families from transmission via yarning sessions and an animation co-developed with TB staff and local community members.[95-97]

Before the Torres and Cape TB Control Unit commenced operating in January 2016, all TB outreach services were delivered from the Cairns TB Control Unit. The challenges presented by the remoteness of the Torres Strait Islands are exacerbated by the inability to service more than two islands per day due to the distance between the islands, and the requirement for pilots to adhere to strict flying times to prevent fatigue risk and comply with workplace heat and safety regulations.[98] The spatio-temporal challenges inherent to TB management in these remote communities have not changed over time but the logistics of health care delivery are now less complex with the Torres and Cape TB Control Unit based on Thursday Island, as staff can now easily do day-trip visits to the surrounding islands by small aircraft to see new patients or missed patients; however, this remains a costly exercise. For example, every resident of the Torres and Cape below the age of five is considered at risk of TB and is eligible for the BCG vaccine. The Torres and Cape TB Control Unit is the only health service in Australia with a remit to vaccinate the entire paediatric population <5years of age. In the Torres Strait in 2018, the minimum cost to administer the BCG vaccine to just one child from an outer island who did not previously receive it as a neonate in hospital, was $1,066 (including travel but excluding vaccine and labour costs), and double that for children who were >6months of age and required a TST 48-72 hours prior to vaccination. The cost to vaccinate children residing on islands without a runway is even higher, as TB nurses can only reach these islands by helicopter.

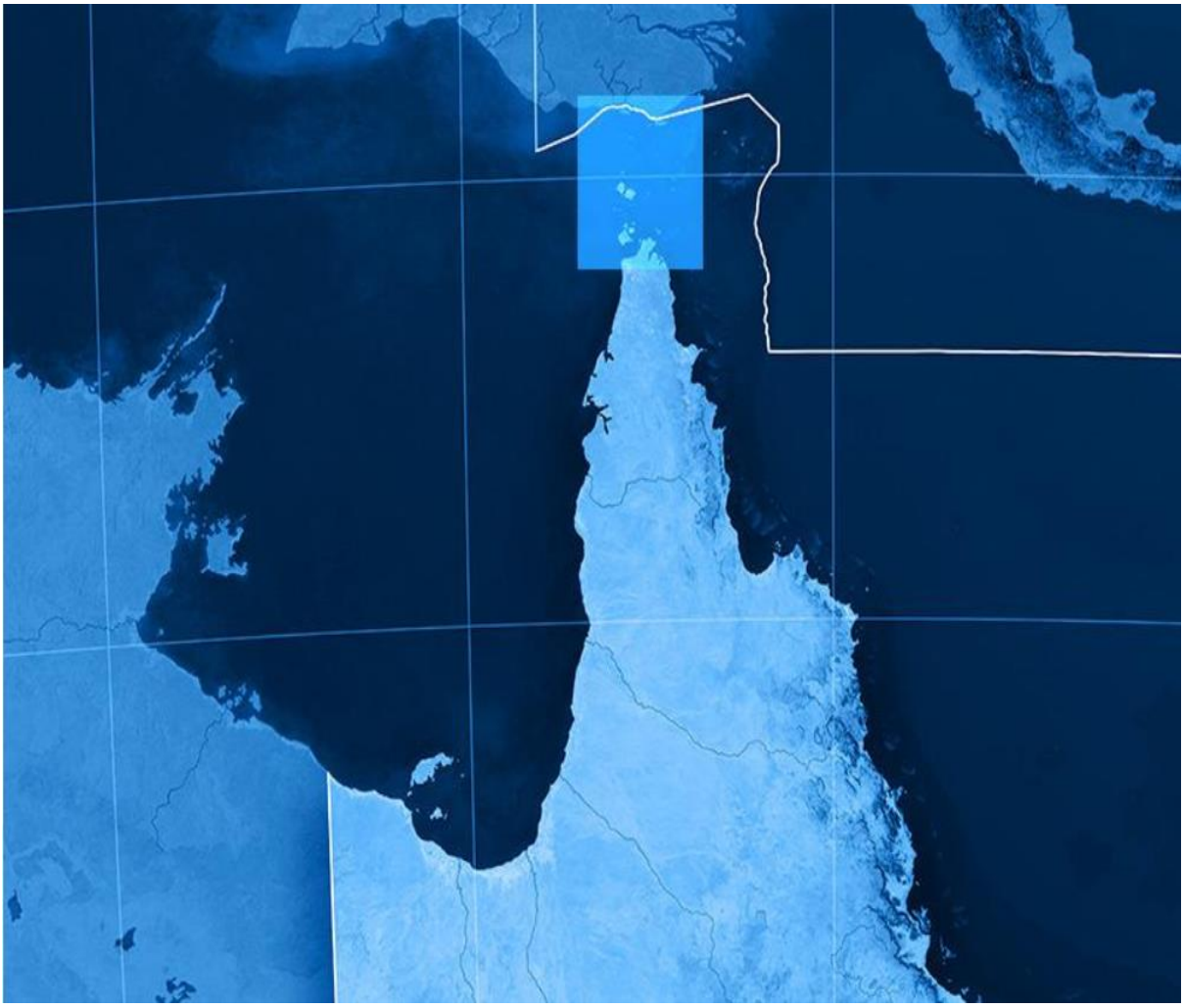


Figure 1.2.10 Map: Australia/Papua New Guinea international border. Source: Australian National Audit Office.[99]

1.16 TB in the Western Province, PNG

> We spend immense sums of money in the prevention of infectious diseases yet we neglect the most deadly of all…we are bound to protect the health of community members against tuberculosis – it is one of the most pressing questions in preventative medicine
>
> - Dr George Lane Mullins, 1898

The PNG-Torres Strait border area (Figure 1.2.10) is potentially a major source of drug susceptible, mono-resistant and MDR-TB into Australia. At the closest point, the Torres Strait Islands in Queensland are less than 5 kilometres from PNG's Western Province. Cross-border dynamics and current TB prevention and control efforts are largely attributable to geographical, regional, political and administrative complexities and structures.

The Torres Strait Islander population of Queensland, who share this international border with the Western Province of PNG are particularly vulnerable to cross-border transmission.[100] The National Capital District, where Port Moresby is located, contributes to 25% of PNG's TB burden[101] with very high prevalence of HIV reported in 2018 in at-risk groups such as female sex workers (14.9%) and men who have sex with men (8.5%).[102] PNG's first case of MDR-TB was reported in 2008 at Daru in the Western Province, with cases numbers reaching 167 by 2015,[101] however, Queensland Health identified MDR-TB in PNG nationals presenting to border clinics many years earlier.[10]

A surge in TB cases, particularly MDR-TB diagnosed in PNG nationals in the Torres Strait Islands presented a critical public health concern.[10] Notably, TB clinicians based in FNQ played an instrumental role in drawing attention to this escalating crisis. Through rigorous documentation, research and publication efforts, these clinicians sounded alarms not only to the Queensland and Australian governments but also to the wider public.[10,103,104] Their compelling findings and consequent advocacy efforts,[105] coupled with the involvement of professional bodies[106] and media coverage by Jo Chandler,[107] exerted significant pressure on the Australian government to deliberate and implement necessary policy actions.

Responding to the emerging policy problem, the Australian government (AusAID), through DFAT, commissioned (Associate) Professor Emma McBryde to evaluate the risks of TB in the Western Province. Both the PNG government and AusAID agreed to all the recommendations outlined in the 'McBryde Report'.[108] The 'McBryde Report'[109] and other articles and academic contributions on the subject led to bolstered TB services in the Western Province[110,111] while AusAID concurrently established methods to enhance the coordination of care of PNG Treaty village inhabitants.

Implementation of multi-faceted paper (AusAID Tackling Tuberculosis in Western Province, PNG (2012)[112] which comprised seven strategic components, sought to offer phased, long-term support for TB control in the Western Province, an effective public health approach to TB management, improved primary health care in PNG, endorsed leadership initiatives by the PNG government, a sustained cross-border endeavour, and a "whole of government" approach, all while ensuring regular reviews and monitoring of progress. Though ambitious, modelling undertaken indicated providing TB aid to the Western Province would be cost effective.[113] Initiatives such as the inception of the Medics Queen, Clinical Collaborative Group, and the Torres Strait Inter-departmental Committee all stemmed from the overarching AusAID project.

Beyond its humanitarian implications, this policy document served a political agenda, striving to prevent TB from migrating across the Torres Strait.

As at 2015, 10 extensively drug-resistant (XDR) TB cases were reported on Daru Island, of which one had achieved cure at the time.[101] Grey literature that was unable to be obtained for the purpose of this narrative review may contain more recent evidence as to patient outcomes or the prevalence of XDR-TB cases on Daru Island.

Although the region of the Western Province of PNG that borders Australia is not a refugee setting and is generally not affected by natural disasters (other than rising sea levels and the occasional cyclone), it is home to an endemic TB context and suffers system breakdowns that are often observed during catastrophic population events in other parts of the world. Health system disruption due to a break down in law and order, and political issues, such as electoral interference, corruption and diversion of funds earmarked for health, are additional challenges that PNG nationals face on an ongoing basis.[114,115]

The closure of DGH from late July to late August, 2018 is an example of the detrimental consequences of public funds diversion. The PNG government committed K18 million to DGH through the National Department of Health in 2015, but these funds did not reach the hospital.[116] The lack of financial support resulted in a deficit of medications, equipment, pathology reagents, masks and wages.[117] Health professionals have long warned of a lack of financial support for health services in the Western Province region (D. Peniyamina, personal communication, April 2016), possibly due to the financial commitment required to support the Australia-Pacific Economic Cooperation (APEC) diplomatic summit hosted by PNG in 2018.

The closure of DGH had ramifications for PNG patients presenting to Queensland Health facilities who required referral to the hospital, located 67.4kilometres away from the northern Torres Strait Islands and accessible only by boat (Figure 1.2.11). The next closest major hospital to DGH is located in Port Moresby, a further 437 kilometres away, which is impracticable to get to by personal boats powered by small outboard motors. Fortunately, the TB Program remained open on Daru during this time despite the closure of the hospital.

Figure 1.2.11 Map: Distance between Saibai Island in the Torres Strait, Australia to Daru Island in Papua New Guinea. Source: Google Maps.

1.16.1 TB on Daru Island

The authors of a large population-based study conducted from 2012-2014 in four provinces of PNG (Madang, Morobe, National Capital District and Western) found that DGH had 30% (6/20) of all new cases of TB, and 33% (8/24) of all previously treated cases were MDR-TB.[118] Across the four areas, MDR-TB was 11-fold more likely in previously treated cases. Up until 2008, limited diagnostic capability were available on the small remote island and enhanced diagnostics were first provided after an Australian delegation visited Daru Island in 2008 to warn of MDR-TB diagnoses being made in Western Province villagers presenting to islands in the Torres Strait. The Australian government's aid program solidified the partnership between DGH and the Queensland Mycobacterium Reference Laboratory in Brisbane to run culture and drug susceptibility testing (DST) on samples that tested positive for TB and rifampicin resistance on GeneXpert from 2012. This partnership and diagnostic support are still available today. Since 2012, the placement of the rapid diagnostic tool Xpert MTB/RIF assay for detection of TB has alleviated diagnostic delays and improved time to treat on Daru.[118] Rapid diagnosis in this setting allowed for patients to commence on standardised empiric treatment regimens while waiting for DST results from Brisbane which, depending on the resistance profile, may then alter regimens.[118]

In 2015, rates of MDR-TB remained elevated with 1% of the population of Daru diagnosed with MDR-TB with this number is expected to rise with the implementation of active case finding.[119] Between 2014 and 2017 in the South Fly District of PNG, the incidence rate of TB decreased from 1031 to 736 cases per 100,000 population and in the same period MDR-TB cases as a proportion of all TB cases increased.[120]

Reasons for the higher prevalence of MDR-TB on Daru may include overcrowding; limited human resources for health to identify and educate patients; high rates of poor compliance, possibly due to early discharge from hospital where patients are vulnerable to relapse; the absence of quality drugs and structure to support supervised treatment; inappropriate isolation of patients, and extreme poverty.[118,121]

In 2012, the AusAID program funded a TB ward that was built on Daru Island with 22 beds including 6 isolation rooms dedicated to MDR-TB / XDR-TB patients. In Australia, TB inpatients remain in isolation until treatment has commenced and clinical and sputum smear results indicate they are non-infectious.[77] On Daru, this is not the case. Patients are generally commenced on treatment in hospital but may still be infectious upon discharge. Prior to the new TB ward, DGH (Figure 1.2.12) had insufficient isolation rooms to cope with demand. Further patients with MDR-TB mixed with patients with suspected XDR-TB, and patients were not always compliant with isolation precautions, often removing their masks and leaving isolation rooms.[122] There have also been instances where anti-TB drugs for patients with MDR-TB were not available, where Daru had to rely on the Australian government to assist with procurement.[123] Similarly, there have been instances where TB programs in Queensland have run out of second line anti-TB medications and stockpiling has been introduced as a preventative strategy to avoid treatment interruption of MDR patients.[10]

Figure 1.2.12 Daru General Hospital (photograph courtesy of Aaron Smith, 2015).

1.16.2 The Torres Strait Treaty

The Torres Strait Treaty is an agreement ratified in 1985 between the governments of both Australia and PNG.[124] The Treaty contains specifications for maritime jurisdiction, fisheries resources, navigation and the islands, and provides protection for local inhabitants on both sides of the border and their traditional activities.[125] Traditional inhabitants of 13 Australian Torres Strait Islands and 13 PNG Treaty villages enjoy cross-border movement without the need for passport or visa, provided the intended travel is for traditional purposes.[126] The area that encompasses these communities is known as the Torres Strait Protected Zone (TSPZ) (Figure 1.2.13). The Torres Strait / PNG region presents unique border and biosecurity challenges for Australian Border Protection agencies and Queensland Health.[126]

The population of the Australian islands in the TSPZ was approximately 4590-4740, based on data collected by the Torres Strait Island Regional Council in 2016.[92] The most recent PNG population census was conducted in 2011 and at that time the Treaty village population was estimated to be 5,619.[127] While the Torres Strait Treaty allows traditional inhabitants to fish and hunt and barter, it does not allow goods to be sold for cash.[128] Residents of the Australian Torres Strait Islands live in council-built houses, have access to island supermarkets, are

entitled to use quality Australian health care services and may access social welfare benefits.[128] One nautical mile away, PNG Treaty villages are among the poorest and most remote in PNG.[129] With the exception of one village close to Australia where homes are partly constructed of tarpaulin and tin sheeting, residents of PNpaG Treaty villages live in overcrowded palm frond huts with no running water or electricity, and where open defecation is the norm. Any income is likely to come from the sale of woven baskets, palm frond brooms, wooden carvings and seafood at markets held on Saibai and Boigu Islands, or via direct employment.[129] Of the 13 PNG Treaty villages in 2016, only 7 had basic medical units and one had a health centre. These facilities are frequently unmanned or unstocked with basic medical supplies.[57]

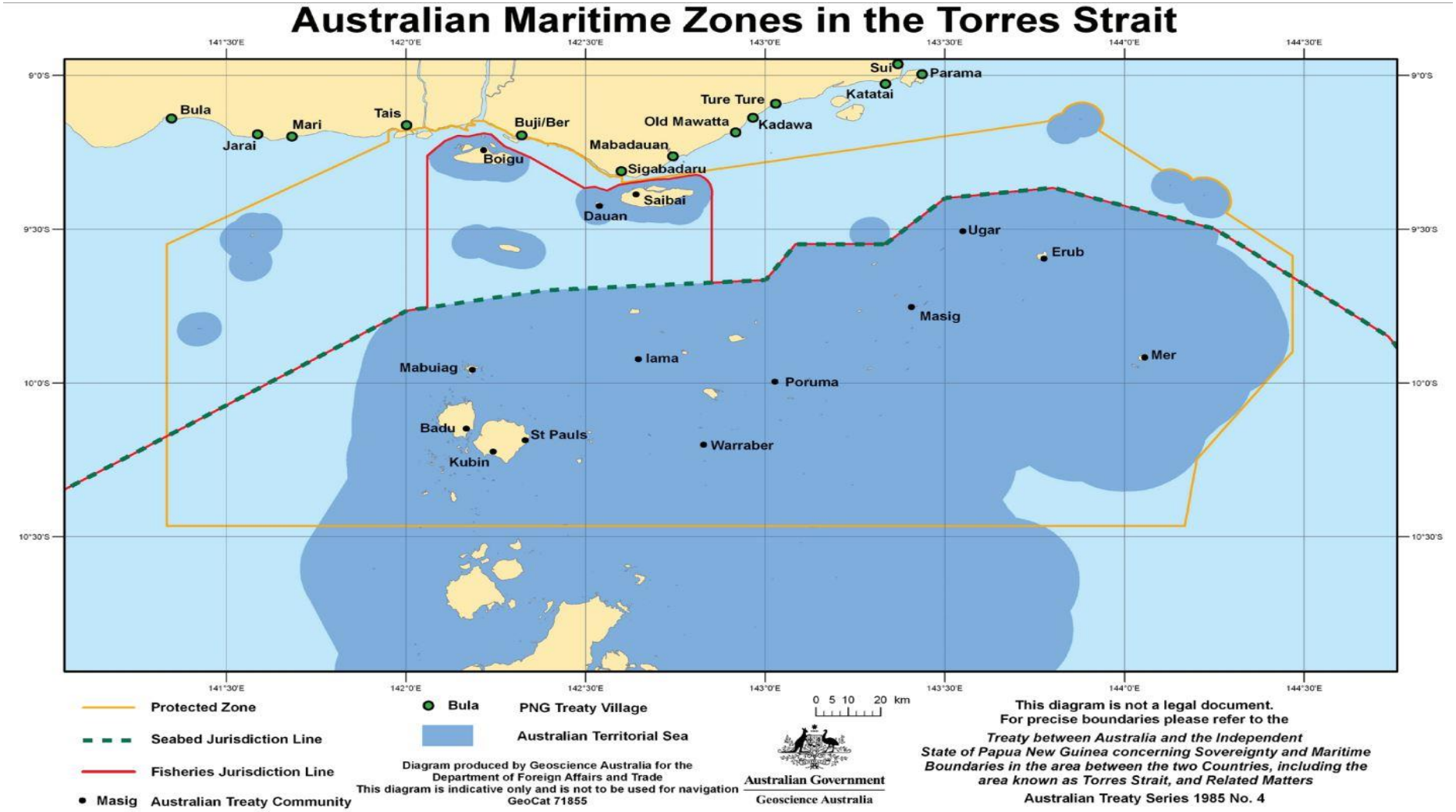


Figure 1.2.13 Map of the Torres Strait/Papua New Guinea border and Maritime Zones in the Torres Strait. Courtesy of the Department of Foreign Affairs and Trade and Australian Fisheries Management Authority.[126]

Health care is not considered a traditional activity, and access to Australian health facilities is not in and of itself a provision for PNG nationals under the Torres Strait Treaty.[130] Great disparities exist in the border region where superior health facilities, running water and electricity are located on the Australian side of the border.[131] Queensland Health triages both Australian and PNG nationals who present to one of the PHCs located on the islands in the TSPZ according to the nature and immediacy of the clinical presentation.[130] According to Australian Border Force, there are approximately 27,000 inward visits annually, not all of which are for health, which places increased burden on the Australian health system. The majority of patients presenting to Queensland Health facilities come from one of the Treaty villages; however, there are also PNG patients who present who do not have traditional visitation rights.[10]

Figure 1.2.14 Boigu Island, the closest of all the Torres Strait Islands to PNG (Foster, 2017).

The maximum time a Treaty Visitor can stay on an island in the TSPZ is three weeks although this can vary across island councils. As at September, 2019, the Torres Strait Island Regional Council representative on Saibai Island limited the number of incoming visitors to 30 per day to aid in the management of local water shortages.[10] Passes are also available to Treaty Visitors who sell handicrafts such as woven mats or wood carvings or have crabs or fish for sale. Treaty

Visit passes are governed and approved by a representative of the Torres Strait Island Regional Council on each island in the TSPZ. The impact of cross-border movement on TB in the Torres Strait is primarily felt by Torres Strait Island residents who unknowingly provide accommodation or employment to visiting PNG nationals with suspected pulmonary TB. Although there is a heightened risk of TB transmission in the region,[10] the disease has not led to any closures of the Torres Strait / PNG border. This is in contrast to closures that have occurred due to water shortages during the dry season or outbreaks due to cholera.[10]

Figure 1.2.15 PNG national leaving Saibai Island and heading home in a small boat (Foster, 2017).

Figure 1.2.16 Message from the Department of Agriculture for PNG nationals arriving on Boigu Island (Foster, 2019)

1.16.3 Geographical and Climate Change Considerations for the Treaty villages

Located primarily in mudflat areas, the 13 Treaty villages - Bula, Mari, Jarai, Tais, Buzi/Ber (considered one village under the Treaty provisions,[99] Sigabadaru, Mabadauan, Old Mawatta, Ture Ture, Kadawa, Katatai, Parama and Sui - are experiencing challenges resulting from rising sea levels.[57] In some instances, communities have relocated a number of times as the changes in the high tide mark have rendered their previous locations uninhabitable. One example of this is Ture Ture village (Figure 1.2.17), where the local population have exhausted all options for further moves as the rising waters have pushed them back against the boundary of another village. In this instance, the rising tides can be marked by a set of church steps located 200 metres out from what is now the shoreline, indicating just how far the waters have risen (Figure 1.2.18). Low tides also present significant challenges for the residents of these villages, as the water retreats so far that some villagers are forced to walk up to two kilometres through mudflats to reach the sea in order to reach their boats. Residents are often devoid of any foot ware and are susceptible to cuts from clam shells buried in the mud. This may then lead to infection which is difficult to treat in these isolated areas.

Figure 1.2.17 Ture Ture Treaty village: Rising sea levels (photograph courtesy of Aaron Smith, 2015).

Figure 1.2.18 Ture Ture Treaty village – the old church steps swallowed by the sea (photograph courtesy of Aaron Smith, 2015).

The Treaty villages are some of the most remote communities in PNG when their distance from the National Capital District (NCD) Port Moresby is considered (C. Harrington, personal communication, December 2014). The distance from the most western Treaty village, Bula to the NCD is over 550 kilometres and with no roads, thick jungle terrain, and the South Fly River separating them - the journey is inaccessible without a boat.

1.16.4 Medics Queen

To minimise some of the costs incurred by patients and assist with improving access for TB patients to DGH, the Australian Government (AusAID) donated a purpose-built sea ambulance costing $486,000 which was delivered to Daru in 2012, called the 'Medics Queen'.[132] To increase the reach, two banana boats were later procured and between 2012 and 2017, 179 outreach activities occurred at a cost of $1.4 million.[133] Activities include mobile outreach clinics and transfer to Daru for further testing and follow up of patients.[134] Although AusAID donated the vessels, it is difficult to ascertain who is responsible for staffing, maintenance and

route allocation. A report published by DFAT in February 2013 states that approximately $15,000 is provided as a package of support for the boat per month and this includes a qualified driver, fuel, services, maintenance and security. However, this does not give an indication of how much the patients are out of pocket and this needs further investigation.

Aside from the belief by many Treaty villagers that the design of the Medics Queen is incompatible with the low-lying mudflats adjacent to most PNG Treaty villages, there have been many examples of poor management of the vessel since it was donated. Issues have included misuse of the vessel for personal activities, misuse of fuel, and failure to visit Treaty villages over many months.[135] AusAID and Western Province Health Authority officials, regularly claim that the boat has not reached the Treaty villages due to it being dry-docked in Daru for maintenance.[135] While the vessel is being serviced, AusAID has stated it contributes two banana boats but do not provide fuel or maintenance for these vessels.[135] The Medics Queen is frequently dry-docked and not functioning, with reports of the cause of this ranging from maintenance issues to the need to recruit a suitable skipper (personal communication, 2015).

When not reportedly dry-docked, the Western Province Health Authority maintains that the vessel is used for emergency health evacuations, TB clinics and treatment, and other routine outreach health services including maternal and child health, antenatal and vaccination clinics, however, Treaty village representatives have raised concerns about the frequency and purpose of Medics Queen visits.[136] In October 2013, representatives from various Australian Government agencies agreed to provide updates on the numbers and purpose of visits made to Treaty villages[136] however if these details have been provided, they have not been made publicly available. Continued mismanagement and inappropriate use of this vessel directly impacts drug supply, impedes rapid case detection, and increases the risk of community-based and cross-border transmission in this region.

Figure 1.2.19 The Medics Queen dry-docked on Daru Island, PNG (Foster, 2019).

Of the 13 Treaty villages, 7 have Aid posts. Aid posts are designed to provide local community members with basic health care, preventative services, first aid in emergencies and treatment of minor conditions. Aid posts should be stocked with dressings, fluids and basic medication including antibiotics and antimalarials, however, these Aid posts are frequently unstocked or unmanned.[57] Restocking from Mabadauan Health Centre is the expected process, which in turn, receive their stock from DGH (D. Peniyamina, personal communication, 2019). However, no resources such as a boat or money for fuel is provided for health staff, which limits their capacity to facilitate collection of medication, supplies or wages.[137]

For service beyond that which an Aid Post can deliver, referral to a Health Centre is required. Mabadauan has the only Health Centre for Treaty villagers, and this is a 20-minute boat journey from Saibai Island in Queensland. The health worker at Mabadauan Health Centre is often unpaid and frequently threatened by non-Treaty villagers to write referral letters for community members to access Queensland Health services (personal communication, 2017). Referral letters across the border are not required but is a process that is common. A simple marking on the referral letter notifies Queensland Health staff that a threat has been made toward the health worker in Mabadauan.

1.16.5 Proposed Improvements to Health Infrastructure in the Treaty Villages

In 2013, Australian and PNG members of the Cross Border Health Issues Committee, were advised that the PNG Government had approved planning for the construction of a new health facility in Treaty village Mabadauan.[136] DFAT committed $10 million toward the construction of this new health facility as well as staff accommodation to support it.[123] Although it was expected that tender for construction would take place in August 2015,[123] with a view for official opening to occur in 2016, there have been ongoing delays due to land issues.[138] In April 2014, the PNG National Department of Health announced that infrastructure improvements had been recommended in three other Treaty villages.[139] This included upgrading existing Aid Posts to Community Health Posts in Bula, Buzi and Sigabadaru, however PNG Government funding was redirected to support the 2017 PNG national elections and preparations for the 2018 APEC meeting to be held in PNG.[138]

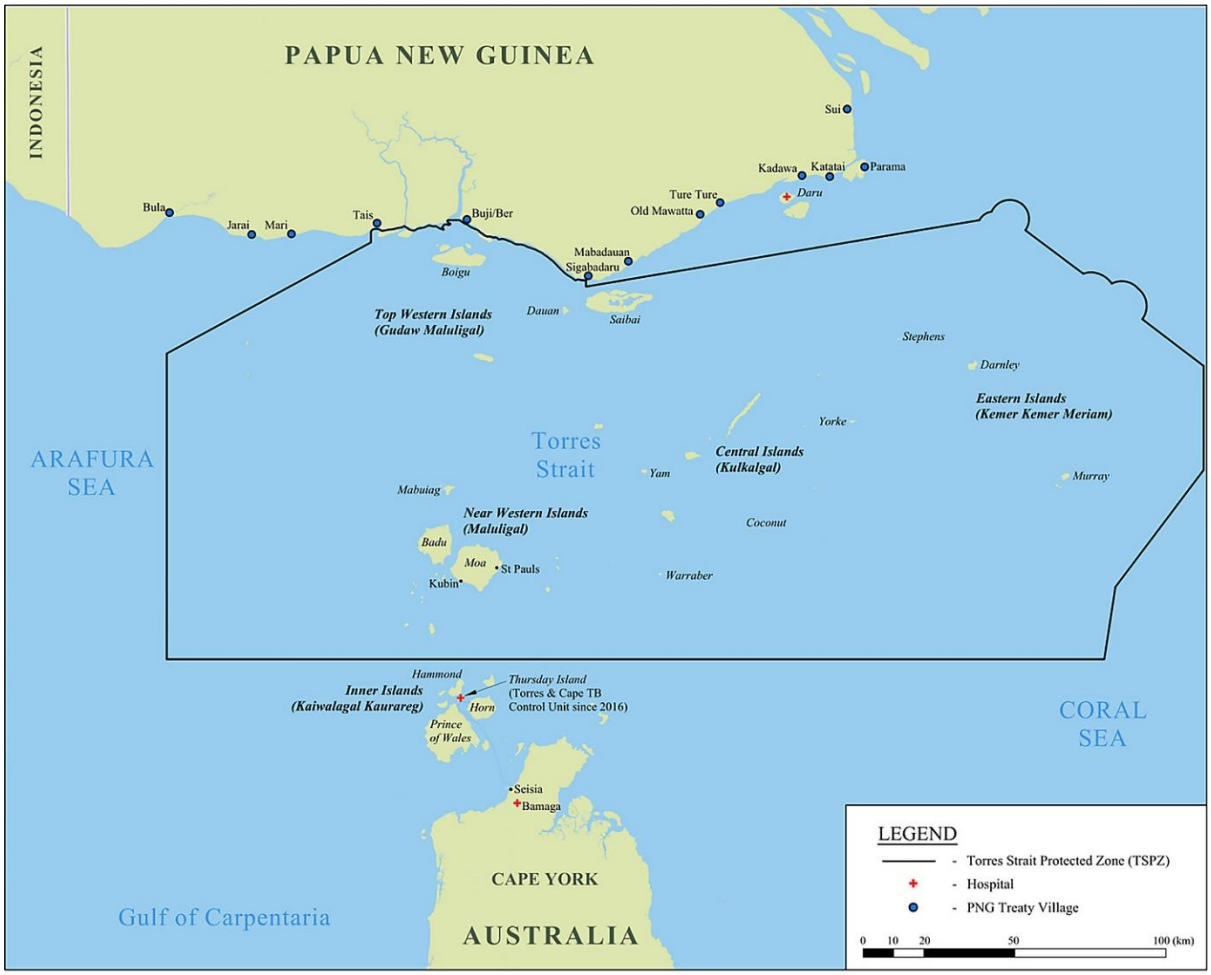


Figure 1.2.20 Map of the Torres Strait/Papua New Guinea cross-border region and locations of medical infrastructure to support TB care in the region.[140]

1.17 Stakeholders relevant to suspected or confirmed TB in PNG nationals presenting to Queensland Health facilities in the Torres Strait Protected Zone

1.17.1 Bilateral

1.17.1.1 Health Issues Committee

Established in 2003, the Torres Strait Cross Border Health Issues Committee (HIC) is a sub-committee of the Joint Advisory Council of the Torres Strait Treaty. Members of the HIC meet biannually to identify and discuss prevailing and emerging health issues and activities pertaining to both sides of the international border region.[141] HIC is co-Chaired by the Australian Department of Health and the PNG National Department of Health, is not funded and requires agency representatives to progress issues identified. Australian member agencies include the Queensland Department of Health, Torres and Cape HHS, Torres and Cape TB Control Unit, Cairns Tropical Public Health Unit, DFAT, Australian Border Force, Torres Strait Regional Authority and Torres Strait Island Regional Council. PNG member agencies include the PNG National Department of Health, Western Province Health Authority, Treaty village Councillors and the Australian High Commission (based in Port Moresby). Other stakeholders include DGH, World Vision, Burnet Institute, Fisheries, Quarantine and the Health and HIV Implementation Services Provider.[141]

Discussions about border TB control are a standing agenda item of all biannual HIC meetings, however, progress of initiatives can be slow. Shortages of PNG Government funding frequently feature at HIC meetings.[142] In 2008, the HIC was asked to develop a 'Package of Measures' to address in part, challenges associated with the management of PNG TB patients and the burden this places on the Australian health system.[143] Some of the recommendations have been implemented such as the redevelopment of DGH complete with a MDR-TB ward, a facilitated cross-border movement process for health professionals to move through non-proclaimed ports, and two-way radios to improve cross-border communication.[143] Other proposed initiatives such as upgrading the Health Centre at Mabadauan and Aid posts in other PNG Treaty villages, have fallen short of expected delivery timeframe, in part due to funding constraints experienced by the PNG health system.[143] Communications in Buzi are non-existent as proposed two-way radios have not been implemented and the Telstra communications tower (Australian communications company) located at Boigu does not reach the western PNG

Treaty villages. Getting messages into Buzi is reliant upon grass roots communication, when Buzi villagers visit Boigu Island and other PNG Treaty villages. The proposed 2015 upgrade of the Buzi Aid post with service capacity for two health workers[143] was reported as stalled due to insufficient PNG funding in 2017[142] and had not come to fruition at the time of writing.

The HIC also directed Queensland Health to develop and implement a broad cross-border policy covering all types of clinical presentations in the TSPZ, which was first published in 2009.[57] A TB-specific cross-border management procedure was developed and piloted, and then published in 2016 with HIC and Clinical Collaborative Group consultation and endorsement but not as an HIC directive. While Policy 0900 *Management of PNG traditional inhabitants presenting to Queensland Health facilities within the Australian islands of the Torres Strait Protected Zone* and its associated procedure and TB screening supplement have assisted Queensland Health clinicians with managing border clinical presentations, referrals and medical evacuation criteria, quantifying the effectiveness of this approach has been difficult. The numbers of medical evacuations of PNG nationals presenting to Torres Strait PHCs decreased by 50% (L. Broad, personal communication, 2019) since policy implementation, however, there is a paucity of published data on patient outcome indicators, including mortality data. Clinical tools such as the Child Emergency Warning Tool (CEWT), Maternal Early Warning Tool (MEWT), Queensland-Adult Deterioration Score (Q-ADDS) and Australasian Triage Score assist clinicians to determine medical evacuation requirements, but **it is unknown how effective these and other tools are when managing patients with presumed TB. Identifying a medical emergency in a patient with presumed TB may not be a case presentation that new or visiting Senior Medical Officers (SMO) have prior experience or expertise in**. This gap in the literature is addressed in Chapters 5 and 6. Plans to update a Memorandum of Understanding (MOU) between Queensland Health and PNG Department of Health was mentioned in the HIC meeting held in Port Moresby in 2013,[136] however no further mention of this MOU has been incorporated into any published minutes or meeting summaries since.

1.17.1.2 Clinical Collaborative Group (CCG)

The CCG was established in 2012 under direction of the HIC to facilitate communication between clinicians on both sides of the border regarding the management, referral and case review of border TB patients. The Clinical Communication Protocol, developed by CCG members, provides up to date contact and transfer information for Queensland-based TB

Control Units, DGH and Western Province Health Authority staff.[144] The Protocol remains an active and valuable document to date despite the CCG being abolished by the Queensland Chief Health Officer without consultation with CCG members in 2016. Without HIC support through the CCG, cross-border communication regarding PNG national TB patients managed in Queensland and who require referral back to the PNG health system has been challenging and has resulted in weakened bilateral relations. Several attempts by the Torres and Cape TB Control Unit to reassemble TB clinician meetings have failed, primarily due to funding constraints.

1.17.1.3 Torres Strait Inter-departmental Committee

Biannual meetings are Chaired by the DFAT Torres Strait Treaty Liaison Office based on Thursday Island and co-Chaired by a representative from the Traditional Inhabitants Meeting. Its purpose is to promote collaboration, and pooling of resources, and ensure that Australian Government Agencies with portfolios in the TSPZ are responsive to the requirements of the Treaty.[143] Member agencies include Australian Border Force, Commonwealth Department of Health, Queensland Health, Australian High Commission, Torres Strait Island Regional Council, Department of Agriculture, Department of Environment and Energy and Queensland Police Service.

1.17.1.4 World Vision

World Vision is a faith-based (Christian) non-Government Organization specialising in humanitarian aid.[145] In the PNG context, World Vision focuses on communicable diseases, sanitation and hygiene, nutrition, gender equality and education.[145] World Vision's treatment supporter training and DOT delivery program on Daru Island has been more successful than efforts in the PNG Treaty villages. According to World Vision, at the five sites across Daru Island where TB patients receive their TB medication with a complimentary lunch, compliance and completion rates have improved.[146] In 2013, World Vision, based on Daru Island, trained treatment supporters located in the Treaty villages to deliver DOT. Some treatment supporters were past patients whereas others were concerned community members. Treatment supporters were paid by the Western Province Health Authority to train, and were advised that they would receive a small stipend for every TB patient they supported through their TB treatment. Following initial training, it has been reported that no stipend was provided to treatment supporters (PNG TB Treatment Supporter, personal communication, September 2015).

Without access to boats and accommodation, the inability to travel the long distances to Treaty villages prevents World Vision staff from re-training and supporting residents providing DOT. The consequences of this lack of continuous support may lead to lower levels of compliance with TB treatment which leaves patients at risk of treatment failure.

1.17.2 Local Stakeholder Portfolios in the TSPZ

1.17.2.1 Cross Border Communication Officer

Since 2008, a federally funded Cross Border Communications Officer (CBCO) has been employed by Queensland Health to facilitate communication between health services in the PNG Treaty villages, the Torres Strait Islands and Daru. Upon discharge of a TB patient from Queensland Health facilities, it is the responsibility of the CBCO to notify DGH of the referred patient and liaise with the Western Provincial Health Office regarding transport options for patients referred back to PNG. Due to unreliable internet and phone lines, this can be difficult for the CBCO to achieve. The CBCO holds a Standing Agenda Item at the HIC and provides monthly stakeholder reports about PNG national patients accessing health services in the Torres Strait.

This position is, and always has been, held by a PNG national who was formerly a Medical Officer in PNG. Referral of patients from the Torres Strait back to the PNG health system are possible because of a designated CBCO.[57] Since the appointment of the CBCO in Queensland in 2008, there have been calls to action for a CBCO to also be located on Daru Island, however, despite frequent requests through the HIC, a CBCO on the PNG side has never been appointed. The CBCO position is crucial for the transfer of patients back to the PNG health system. Appointment of a CBCO on the PNG side would greatly enhance cross-border communication and provide Queensland Health clinicians with real-time patient outcome data that could provide an insight into the outcomes for patients referred back to PNG.

1.17.2.2 Department of Foreign Affairs and Trade (DFAT)

DFAT are responsible for ensuring a whole of government approach to the provisions of the Torres Strait Treaty.[143] This includes cooperation and coordination on both sides of the border to address issues pertaining to law and order, economic development, health, conservation, border protection and biosecurity.[143] A DFAT Treaty Liaison Officer, located on Thursday Island coordinates biannual Treaty Awareness Visits to the Treaty villages for multiple

Australian Government agencies with portfolios in the TSPZ. These visits provide opportunities for agencies to communicate relevant agendas to Treaty villagers and provide a platform for Treaty villagers to have concerns or issues addressed.[143] DFAT has been instrumental in providing access for the Torres and Cape TB Control Unit to visit the Daru TB Program to strengthen relationships and facilitate information exchange.

1.17.2.3 Australian Border Force (ABF)

Based on Thursday Island and throughout the Torres Strait Islands, ABF uses intelligence-led approaches to assess, analyse, interpret and act on information pertinent to protecting Australia's borders from unauthorised activity. In the TSPZ, ABF has Movement Monitoring Officers who are responsible for determining reasons for movement under the Treaty and refusing entry for unauthorised visitors.[143] Queensland Health has a responsibility to notify AFB of all patients who are medically evacuated to Thursday Island Hospital and beyond, as well as those who are en route back to PNG from an Australian health facility location outside the TSPZ. Queensland Health issues Medical Alerts to ABF where a PNG national refuses to leave the Torres Strait and may pose a public health threat to residents of the Torres Strait. It is important to note that although there is an expectation to notify ABF in such instances, they do not have clearance to forcibly remove or detain any PNG national in the TSPZ, irrespective of whether they are overstayers or a public health threat to island communities (J. Ross, personal communication, 2019). Under the *Migration Act* in 2009, Movement Monitoring Officers are lawfully permitted to approve entry for Treaty Visitors as well as refuse entry and detain unauthorised visitors[147] but PNG nationals with Treaty visitation rights are not considered to be unauthorised visitors while in the TSPZ. ABF are also the custodian of the Facilitated Cross Border Movement agreement which allows health professionals to use non-proclaimed ports, which are ports that are not recognised as a port of entry into Australia, to visit Treaty villages.[143]

1.17.2.4 Torres Strait Island Regional Council (TSIRC)

The TSIRC is located in Cairns and Thursday Island, with offices on each of the Torres Strait Islands where one elected officer is responsible for overall local governance of each of the Torres Strait Islands. The point of difference between the TSIRC and other local government councils in Queensland, is that they are also responsible for law and order and community safety through community police, as well as delivery of housing, employment and border

security functions.[143] In the TSPZ, TSIRC issue Treaty Visitation passes to residents of the Torres Strait Islands and are authorised to determine numbers of incoming PNG national Treaty visitors.

1.17.2.5 Reef and Rainforest Research Centre (RRRC) and In-Loc

Specialising in environmental science and sustainable natural resource management, RRRC is involved in multiple projects in tropical north Queensland and PNG.[148] In 2015, RRRC piloted the 'Building Resilience in Treaty Villages Program' which was a community-driven project sub-contracted to In-Loc, an organisation that specialises in operations management, logistics and training in harsh and remote environments.[58,149] The capacity building-based program was funded by DFAT and the primary base located on Paho Island adjacent to Mabadauan Treaty village. Both male and female PNG rangers were nominated by their communities, paid a wage and trained to implement measures to improve clean water access, storage and sanitation, as well as first aid and disaster response within the Treaty villages.[58] Rangers were also trained in construction, boat handling, leadership and business skills.[58] Australian clinicians at Saibai Island PHC report that many lives have been saved since rangers have been working in the Treaty villages. First aid training has rendered rangers capable and skilled first responders, particularly for stabilising patients bitten by snakes (T. O'Brien, personal communication, 2019). Although the Ranger Program utilises Maritime approved Hooker boats which meet Australian maritime safety standards, transporting patients is not part of the Program's remit. Queensland Health however, has sparingly called on the Ranger Program to assist transporting patients to Daru since 2015, however, this is only possible when the boats are already on a supply run. Given boats allocated from Western Health Provincial Office can be unreliable, it would be beneficial if RRRC boats were funded to assist transport patients from Treaty villages to Daru.

1.18 TB-related Policy Makers

1.18.1 Australian Commonwealth Department of Health

The Australian Strategic TB Policy is written with the goal to achieve national targets that also meet the recommendations provided by the WHO End TB Strategy. There is evidence of national policy commitment to the management of TB in Indigenous populations, but ensuring a transition from national policy development to implementation and governance falls outside

the remit of the National TB Advisory Committee (NTAC) and hence, there is no requirement for TB Units to provide evidence of adherence to the Australian Strategic TB Policy.

Through the Australian Strategic TB Policy, NTAC acknowledges that TB is an issue at the Australia / PNG international border, and calls for increased political commitment and financing related to TB policy. Objectives are generic and there are no specific targets provided by the national government that support the management of cross-border TB. There is no requirement for local TB programs to report indicators or milestones or adherence to any of the statements listed in National TB policy.

As TB management is on the agenda at a federal level, and as the Federal Member for Leichhardt is the Chair of the International TB Caucus, the Torres and Cape TB Control Unit have been provided the opportunity to meet with and receive support from the Special Envoy for TB from the United States of America.

1.18.2 Queensland Health

In 2013, the oversight of TB Control Units in Queensland was decentralised and HHSs became their own Statutory Authorities. At this time, responsibility, development and governance for policies and procedures was relegated to individual HHSs, including all that related to the management of patients at the Torres Strait / PNG international border. From 2013, the Communicable Diseases Branch within Queensland Health relinquished responsibilities pertaining to the governance and management of cross-border TB care. Further, there is not and has never been, representation from within the Communicable Diseases Branch on the Cross Border HIC.

The Queensland Department of Health Communicable Diseases Branch (CDB) has a dedicated team that assists TB Units with high-level issues (i.e. overseas BCG vaccine acquisition, storage and analyses of TB case notification data, facilitation of anti-TB drugs procurement for the state etc.) and are the custodians of the Health Service Directive (HSD)[150] and Protocol[75] for TB control and clinical guidelines. These policy documents describe mandatory requirements and roles and responsibilities for the Queensland Department of Health, HHSs and for TB Control Units in Queensland. When the clinical management of TB has the potential to impact other government or non-government organisations or where there is a risk of increased media attention, TB Units are required to notify the CDB. Otherwise, there are no requirements for TB Units to provide evidence direct to the CDB that the HSD and Protocol

has been implemented. Within the HSD and associated protocol, there is mention of TCHHS-governed cross-border procedures however, the CDB as the System Manager, are not involved in revisions of TCHHS-governed documentation, nor provide assistance to the Torres and Cape TB Control Unit when adherence is not achieved. Hence, there is relative freedom for TB Units in Queensland to design their programs according to their epidemiological and risk profiles.

Stakeholder complexities and remote area challenges associated with the management of TB in the Torres Strait which includes both an Indigenous population and international setting, are not factored in to published guidance at state and federal levels. It therefore falls to local TB units to implement policy that is specific to the unique set of circumstances in their region.

1.18.3 Torres and Cape Hospital and Health Service

The TCHHS cross-border related Policy and Procedures were widely consulted on, both internally within TCHHS and with external stakeholders, with portfolios in the Torres Strait Protected Zone - a complete list of policy and supplementary documents are available in Appendices J2 – J10 although not all documents were permitted by the TCHHS Health Service Chief Executive to be published within this thesis.[88,93,151-157] Policy 0900 and Procedures 1244 and 0222 are commonly referred to in this thesis. Each document was developed within TCHHS, and are owned, authorised and governed by TCHHS. Procedure 0222 is the TB specific cross-border procedure (0222), which was consulted on by the Cross-Border CCG (dismantled in 2015) and the HIC among others. However, the CDB and the HIC do not have oversight or responsibility in regards to this document.

TB Units in Queensland do not sit within or under Public Health Units. For example, the Cairns TB Control Unit is completely separate to Cairns Tropical Public Health Services, as is the Torres and Cape TB Control Unit. At the time of writing, TCHHS do not have an established Public Health Unit outside the responsibilities of the COVID-19 pandemic.

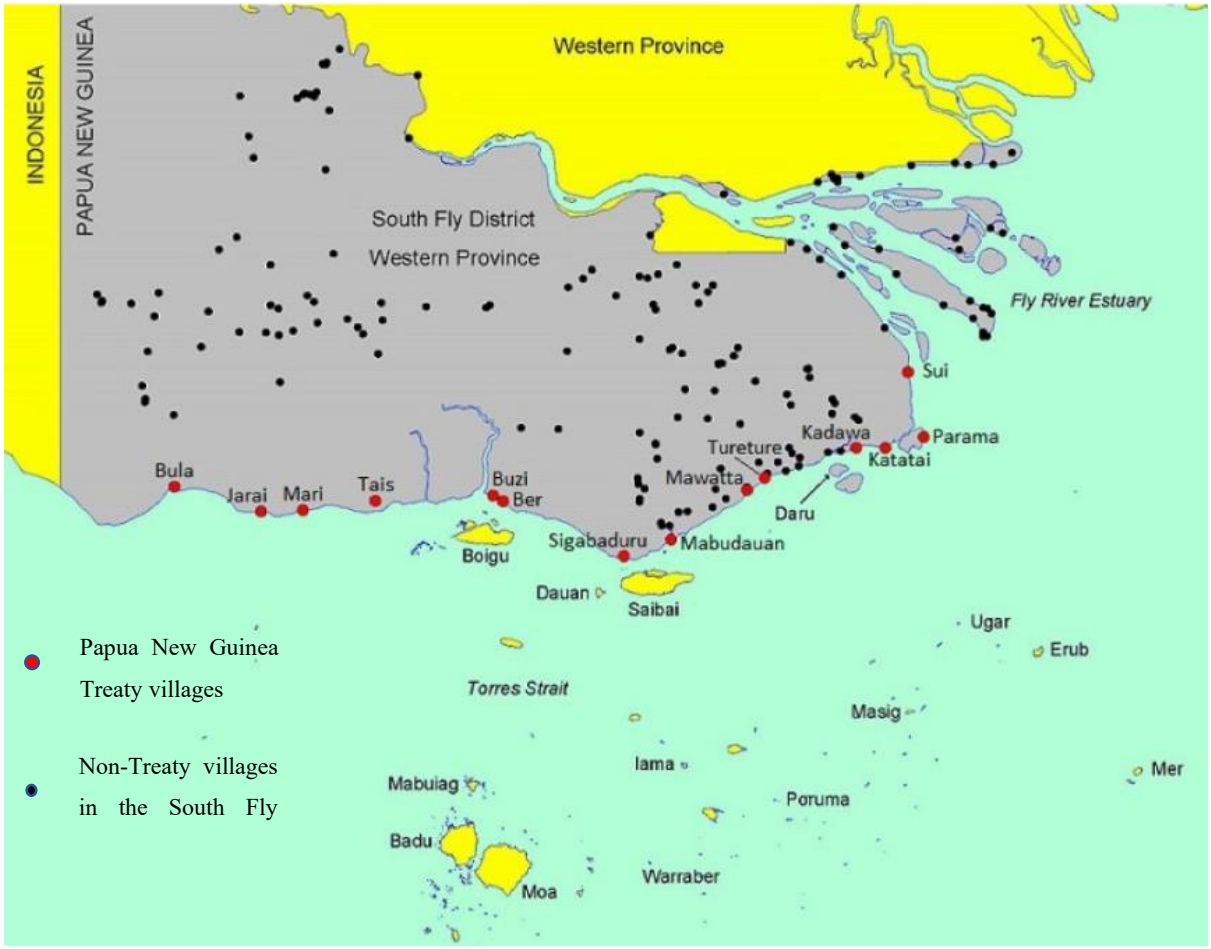


Figure 1.2.21 Map: Torres Strait Islands in the Torres Strait Protected Zone and Papua New Guinea Treaty villages. Source: Courtesy and with permission from Dr Garrick Hitchcock.[158]

1.19 Torres Strait / PNG Border Literature

There is very little information published about conditions and risk factors that may contribute to a high risk of TB disease transmission or programmatic challenges for this cross-border population. Of the published literature available, many are descriptive studies of routinely collected surveillance data, which either focus on either TB in PNG nationals in the Western Province or TB in Australian nationals but rarely both. Few studies provide epidemiological or programmatic insight beyond crude numbers. This paucity of literature available indicates large research gaps regarding risk factors and effective programmatic management as they apply to TB control in the Torres Strait / PNG border region. For example, the formidable risk that overcrowding poses for TB transmission is briefly mentioned by one study[118] but further explanation about socioeconomic deprivation, housing density or numbers per household are not provided. Similarly, various studies offer poor nutrition as a possible explanation for

disproportionate numbers of TB in the Aboriginal and Torres Strait Islander population[30,103,159] but do not explore the relationship between TB and poor dietary intake any further.

1.19.1 TB / Comorbidities

Within the Australian Indigenous population, renal disease, diabetes, and heart disease have a higher prevalence[100] and management of drug-resistant TB (DR-TB) is often complicated by coinfection with other communicable and non-communicable diseases.[160]As has been described in epidemiological studies in Pacific island countries, HIV is unlikely to be a major contributing factor to TB transmission dynamics in the region[42] and does not appear to be a driving force to explain the TB epidemic in the South Fly District of PNG,[43] however due to well-known complications in TB/HIV coinfected patients, HIV testing is standard practice in the Torres Strait / PNG border region.

In the Torres Strait / PNG border region, it is unknown what effect comorbidities have on patients with TB. In other settings, studies have shown that patients with TB and comorbidities are more likely to have poor outcomes.[161-163] Many studies have reported high rates of mortality in patients with renal impairment / TB coinfection.[164-167] In patients with renal / DR-TB coinfection, adverse drug reactions are common and may lead to treatment interruption and poor prognosis.[168]

Delayed diagnosis of TB is also a possible reason for poor prognosis in renal patients[167] and the culmination of diagnostic delay may worsen nutritional status of patients.[164] As uremic symptoms like fever and weight loss are non-specific symptoms of both TB and renal disease, renal physicians practicing in the region would be well placed to consider TB as a differential diagnosis and monitor patients with insidious onset of these symptoms.[167] It is important to note that peritoneal dialysis and haemodialysis are not available for patients with chronic renal failure residing in PNG villages closest to Australia, but a dialysis unit commenced operations at Thursday Island Hospital in 2014 for residents of the Torres Strait.

There is a paucity of recent data available describing the prevalence of diabetes in PNG[169] however the WHO estimates the global burden of diabetes in the adult population is 422 million cases.[170] TB / diabetes coinfection has an increasing prevalence in PNG and is known to increase the risk of TB two to three-fold.[171] The prevalence of type 2 diabetes in residents of the Torres Strait is reported to be the highest in Australia.[172] In other international border settings such as at the South Texas / Mexico border, diabetes surpasses all other risk factors

associated with TB – increasing the risk of reactivation in those exposed to TB.[173] Unfavourable outcomes in diabetic patients with drug susceptible TB (DS-TB) has been previously reported.[174] Although there is limited data describing outcomes in diabetic patients with DR-TB,[175] smaller studies have described an association between diabetes and MDR-TB,[176] and increased frequency of cavitation, lower lung lesions and multidrug-resistance in older diabetic patients with pulmonary TB.[177] There have been no previously published data describing the impact of diabetes on patients with TB in the Torres Strait.

Seropositivity rates of human T cell lymphotrophic virus 1 (HTLV-1) have been reported as endemic in the Indigenous population of Central Australia[178] and were first identified using a serologic survey in a small hunter-gatherer population in the PNG highlands where up to 14% of the population tested positive.[179] Some authors report an association between immune dysregulation caused by HTLV-1 and the high prevalence of active TB disease in Japan, the Caribbean, South America and sub-Saharan Africa,[180,181] however Seaton, Wembri and Nwokolo[182] conducted further serological testing in PNG and found no association between HTLV-1 and TB disease in both pulmonary and extrapulmonary patients. This could be due to differing molecular subtypes, with HTLV-1 subtypes b, d-g found in African populations and HTLV-1 subtype c which appear to be located in remote pockets in the Melanesian / Australian region.[183] While it is possible that HTLV-1 is a risk factor for TB disease progression in Torres Strait and Treaty village populations, this has not been identified in the literature.

Other risk factors which have not been explored in the Torres Strait / PNG border region are the effects that smoking, excessive alcohol use, betel nut consumption – a psychoactive substance - and the use of woodfires for cooking have on patients infected with TB. These are factors that are prevalent in PNG and may contribute to an increased risk of both latent TB and active TB disease.[184] Both active and passive smoke inhalation may reduce the activity of alveolar macrophages, lead to immune dysregulation of pulmonary lymphocytes and interrupt pulmonary dendric cell development.[185] Immune dysregulation may also occur, although the pathophysiology is less clear, in people who consume >40 grams of alcohol per day.[186] Alcohol consumption is most commonly a social activity and can derail TB treatment adherence, and the aerosolization of betel nut juices when expectorated from the mouth may lead to localised transmission of TB among family and social groups.[184] There is considerable scope for further investigation of these issues in the region to inform local public health strategies and messaging.

It is likely that these risk factors have not yet been explored comprehensively in the region due to remoteness of location, logistical difficulties, limited networks, and cultural reasons that prevent access for researchers to develop an in-depth understanding of the Torres Strait / PNG border population. **Furthermore, the absence of literature highlights that there is considerable scope for future analysis as well as opportunities to conceptualise, operationalise and measure the impact of various risk factors on the management of TB.**[187]

1.19.2 Biological Markers and Immune Dysregulation

Various biomarkers such as lymphocyte, haemoglobin and albumin levels have been used to predict severity of disease, immunodeficiency and decreased survival in TB patients.[188] In particular, host immune responses in patients with DR-TB may be associated with poor outcomes.[189] In the Torres Strait / PNG region, the role of biomarkers in both drug-susceptible and DR-TB patients is unknown and warrants investigation.

1.19.3 Lymphocyte levels

Low lymphocytes levels have been reported as an immune abnormality which may suppress the host immune response in patients diagnosed with DR-TB.[189] Suppressed T-lymphocyte function has been observed in guinea pigs with protein deficiency however, there is limited literature available on the effects of micronutrient deficiencies and undernutrition on immunity in humans.[190,191] In the Torres Strait Islander population, high levels of undernutrition (dietary deficiencies as a result of insufficient caloric intake) have been reported.[192] Regardless, it is reasonable to suggest that patients who have had TB for sustained periods would present with overall health decline and that low lymphocyte levels could be a marker for severity of TB disease.[193] A multi-centred study conducted in geographically diverse settings reported a significant association between low lymphocyte levels at baseline and treatment failure.[194] The authors suggested that TB patients with low lymphocyte levels at baseline frequently also have elevated white blood cell counts, which are both indicative of sustained inflammatory responses.[194] **Further investigation is required to ascertain if there is an association between lymphocyte levels and outcomes for TB patients in the Torres Strait / PNG border region, and if routine monitoring of white blood cell counts in DR-TB patients with low lymphocyte levels at baseline, may help to improve treatment outcomes.** This is addressed in Chapter 4.

1.19.4 Haemoglobin levels

The primary function of haemoglobin as an iron-containing protein, is to assist in the carriage of oxygenated blood from the lungs to the tissues.[195] Low haemoglobin has been associated with unfavourable outcomes in TB patients, as well as delayed sputum conversion at two months.[196] In a Brazilian study of 328 TB cases, 61.2% of cases had anaemia and of those, 6.2% had severe anaemia.[197] In Ethiopia, MDR-TB patients with low haemoglobin levels (anaemia) were more than twice as likely to have unfavourable TB treatment outcomes when compared to patients without anaemia.[198] In a study conducted in an ICU setting, serum haemoglobin and albumin were strong predictors of mortality.[199] **There is no literature describing haemoglobin levels in residents of the Torres Strait Islands or PNG nationals living adjacent to the Torres Strait nor their impact on outcomes for patients with TB.** This is addressed in Chapter 4.

1.19.5 Albumin levels

Hypoalbuminaemia has been reported as one of the most sensitive markers of nutritional status and severe malnutrition[200] and has been shown to cause immune dysregulation.[188] Ting and Norton reported evidence of malnourishment and muscle wasting in all Treaty and non-Treaty village children admitted to Townville Hospital in FNQ with central nervous system TB.[201] Although a study in Taiwan found that poor prognosis in culture-confirmed disseminated TB was more likely observed in patients with albumin >3.5 g/dL,[202] studies conducted in China and Israel have reported an association between hypoalbuminaemia and poor prognosis in DR-TB patients.[203,204] Malnutrition may contribute to an increased risk of death in both HIV positive and HIV negative TB patients.[205] In a study of 111 children with MDR-TB, malnutrition at diagnosis was an independent predictor for an outcome of death (OR 15; CI 1.17-192.5; *p* .04).[206] Although there are multiple studies investigating the association between TB and nutrition with contradictory results and inconclusive aetiology, the weight of the evidence favours poor nutrition as an important risk factor in mortality and morbidity from TB in resource poor and impoverished settings.[207]

Protein and micronutrient deficient diets are associated with lowered resistance to infection which in turn increases susceptibility and severity of TB disease.[207] There is some evidence to suggest that vitamin C increases antibacterial effects of rifampicin and isoniazid against TB.[208] Whilst there is limited literature describing the benefits of vitamin C in patients with rifampicin

resistance, it is possible that vitamin C supplementation may play a role in improving sputum conversion for patients with low haemoglobin, and possibly in DR-TB patients with low-level isoniazid resistance who are prescribed high-dose isoniazid.[208] Overall, nutritional supplementation and regular monitoring of serum blood levels may assist with nutritional correction and guide TB programs to improve the management and outcomes of DR-TB patients in the region. Prospective studies that include nutritional supplementation together with routine monitoring of serum biomarkers throughout treatment for DR-TB may be worth consideration.

1.20 TB Control in the Torres Strait / PNG Border Region: (pre-COVID-19 pandemic)

Following a gap analysis and community consultation and feedback during a joint visit from Queensland Health and DFAT representative conducting a community TB education campaign in 2015 in the Torres Strait Islands, a local TB Control Unit was established on Thursday Island in January 2016. Over the past 20 years there have been four different TB models of care in the region (Figure 1.2.22). Prior to the Torres and Cape TB Control Unit commencing operations in the remote region, the Cairns TB Control Unit, 802 kilometres away due South, was responsible for TB control activities in this cross-border region through remote outreach clinics and TB clinics on Saibai and Boigu Islands.

There is limited published information available to describe TB control between 2000 and 2005 however, patients from both the Torres Strait Islands and adjacent PNG villages were medically managed for TB by remote outreach services courtesy of the Cairns TB Control Unit. PNG patients that presented to outreach clinics on Saibai or Boigu Islands between 2006 and 2012 could get full diagnostics and treatment for TB, in addition to outreach TB services provided to residents of the Torres Strait Islands. After the clinics closed in 2012 and until this day, PNG national patients that present to health facilities in the TSPZ with presumptive TB and do not require aeromedical evacuation, are diagnosed in the Torres Strait and referred to the TB Program established at DGH on Daru Island.

From 2006 to 2012, Cairns TB Control Unit held monthly TB clinics on two of the Australian islands closest to the PNG border.[209] To encourage access to the service, fuel vouchers were available to PNG nationals,[10] however despite this initiative, treatment interruptions were commonplace.[9] Attendance at the clinics were often hampered by weather or patients needing

to meet other responsibilities, and logistical problems, at times, disrupted the outreach clinics.[9] Treatment compliance was problematic, with many patients missing doses or not collecting their medications. Between 2000 and 2014, only 31.5% of PNG border patients with MDR-TB successfully completed treatment and only critically ill patients who were medically evacuated to an Australian inpatient facility received second-line injectables.[9] Anecdotal evidence from medical professionals working in the region at the time, suggests that once patients felt better on treatment, the remainder of drugs were sold on the black market or given to other family members suffering from signs and symptoms of TB. The program was closed by the Queensland Government in 2012 due to the risk of the development of drug resistance.[109]

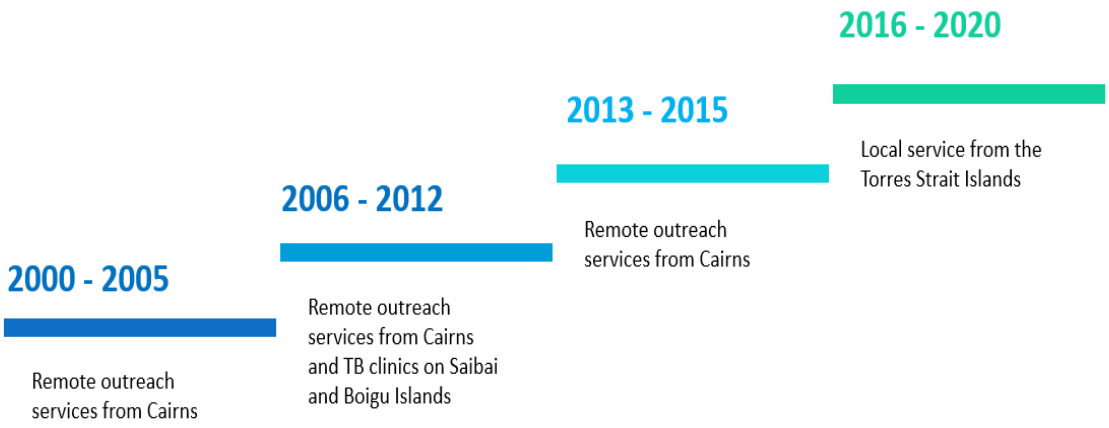


Figure 1.2.22 Models of TB care in the Torres Strait between 2000 and 2020

The Torres and Cape TB Control Unit have implemented a number of initiatives to enhance case detection and improve management of TB in this border region. TB education that is both proactive and reactive is provided. Proactive education includes providing in-services to new staff, new-graduates, open invitations to HHS-wide education for clinicians as well as specific education sessions within PHCs. TB education is available upon request for other Government agencies working in the TSPZ. TB Control Unit staff also provide TB education in collaboration with TSIRC meetings held in community. Biannual visits to the Treaty villages in collaboration with DFAT, have allowed TB Control Unit staff to provide culturally appropriate TB education to Treaty villagers and aid in dispelling myths frequently associated with the disease.

Reactive education refers to that provided by TB physicians to individuals and families upon diagnosis of a TB case which is delivered either in-person or via telehealth. Patient specific education is ongoing for patients on treatment and TB Control Unit staff provide instruction and support to treatment supporters providing DOT for patients. To assist with treatment compliance, the TB Control Unit has also collaborated with some Island Board of Industry Service grocery stores and introduced food voucher incentives for some patients.

Based on the region's TB risk-profile, the Torres and Cape TB Control Unit have implemented health worker screening to ascertain baseline results via the TST or by using IGRAs. Selection of which test to use (if any) to determine baseline results is based on logistics and the location of the staff member at the time of testing. Annual follow-up testing is offered, as well as screening in the event of a known exposure. Screening is also offered to employees working in other Government agencies with a portfolio in the TSPZ.

In 2017, the BCG vaccine was made freely available to all medically eligible PNG nationals born in Thursday Island Hospital. It was also available for medically eligible PNG children <5 years of age who are inpatients at Thursday Island Hospital or outpatients of health facilities in the TSPZ. Outpatient use is limited however, due to high turnover of staff on outer islands, leading to a paucity of staff trained and credentialed to administer the vaccine. This may be improved with a change in regulation to allow suitably qualified Indigenous Health Workers to administer the vaccine.

In 2016, the Torres and Cape TB Control Unit implemented a procedural document – *Management of Papua New Guinea Nationals accessing healthcare within the Australian islands of the Torres Strait Protected Zone, presumed to have or diagnosed with tuberculosis* (otherwise known as the Cross-Border TB procedure), the first of its kind.[210] This document was a result of consultation with clinicians who were confused by what was required for patients suspected as having TB, as well as consultation with local Indigenous stakeholders who were concerned about transmission risk from patients with suspected pulmonary TB remaining in-community in the TSPZ.

The Cross-Border TB procedure and supplement documents (Appendices J2 – J5)[151,152,155,156] provides clear instructions for clinicians regarding the clinical management of patients as well as referral back to the PNG health system. The procedure allows for enhanced detection of HIV/TB and other co-infections, and enables staff to identify close contacts in both Australia

and PNG who may benefit from contact screening. Any Torres Strait Island resident identified as a close contact of a PNG national diagnosed with TB, is invited by the TB Control Unit for screening. In 2018, forms associated with the procedure were translated into Tok Pisin – an English-based and phonetic language, one of the statutory languages of PNG and its lingua franca - to improve communication at the border.

The Australian – PNG border has different TB management policies for the two adjacent countries. The BCG vaccine is available to all residents of the Torres Strait Islands from birth but at the time of writing, was not provided by PNG Health to residents living in the Treaty villages. Australia uses loose anti-TB medications while PNG uses a fixed dose combination (FDC).[211] MDR-TB patients are treated with different second line drugs in each country, and while these are equivalent, specialist advice must be sought when transfer from Australia to PNG is required. The DOT strategy was adopted in PNG in 2000 (though only reached the Western Province in 2012) and included the provision of FDC drugs which reduces the number of pills a patient has to take each day and minimises the risk of patients resorting to self-administered monotherapy.[121] According to the principles of the DOT strategy, each patient diagnosed was to be provided a TB kit containing their full treatment regimen to be taken back to the village where a volunteer treatment support partner would ensure adherence.[121] While this approach had some success on Daru Island where the provincial hospital is based, its implementation elsewhere did not.[121] Due to a lack of drugs available for PNG patients, some FDC kits were shared among two or three patients.[121] Further, FDC therapy did not extend to regimens for children and while it has been reported that some loose drugs would historically get sent home with children, it was not the full regimen and community-based health facilities did not keep additional stock.[121]

DOT was increased in the TSPZ after an audit which showed an increase rate of 35.9 TB cases per 100,000 population and unfavourable treatment outcomes in Indigenous Australians in FNQ.[103] From 1993 to 1997, only 21% of TB patients in FNQ received DOT and in 1998 to 2002, this increased to 73% of active cases.[103,212] While this literature search did not reveal more recent DOT efforts in Indigenous Australians in FNQ, 100% of Indigenous patients in the TSPZ diagnosed with active and latent TB have received DOT since January 2016. Complementing this approach was remote case management, and later, video-DOT. In the absence of expert consensus on treatment for latent MDR-TB, and where modelling has

consistently demonstrated cases attributed to community transmission,[213] DOT is an important reduction strategy for managing both primary and secondary disease.

For PNG national patients who present to the Torres Strait Island health facilities, Queensland Health provides diagnostic and stabilising services for a large variety of clinical presentations including TB, however most patients are referred back to the PNG Health System. All specimens for TB suspects in this region are sent to the Queensland Mycobacterium Reference Laboratory in Brisbane for bacteriological confirmation.[10] There is a microscope available in Mabadauan Treaty village, located 15 minutes by boat from Australia however, as there is no electricity and no microscopist, it cannot be used to its full capacity.

Passive case finding (based on symptomatic presentation) is core business and is available to patients presenting to PHCs in the Torres Strait (Appendices J9 and J10).[88,93] Passive case finding is also core business offered in Aid posts and basic medical units in the PNG Treaty villages. However, contact tracing and screening of close contacts of index cases is available in the Torres Strait but not in the Treaty villages. Since 2016, the Torres and Cape TB Control Unit have conducted contact tracing of PNG patients presenting with signs and symptoms of TB and shared this information with the Daru TB Program, however, as testing close contacts is not part of the Daru TB Program remit in the Treaty and non-Treaty villages (Figure 1.2.21) adjacent to Australia, it is unknown what role close contacts may play on the transmission risk in these villages and in the Torres Strait.

A study analysing Queensland Notifiable Conditions System TB data from 2005-2014 reported a disproportionately high rate of TB in cross-border children diagnosed in Queensland.[159] Many PNG children diagnosed with TB have a parent or close family member with TB yet contact screening does not take place and isoniazid preventative therapy is not available for PNG children in urban settlements or remote rural areas.[121] On the other hand, if a Torres Strait Island resident presents with signs and symptoms of TB they are provided free access to diagnostics, treatment and isolation in an Australian facility.

PNG nationals suspected of having TB in the Treaty villages are generally referred by village health workers to a Queensland Health facility for diagnostics and care which is often followed by a referral to DGH. As well as providing TB services for residents of the Treaty villages, DGH is also the referral hospital for the majority of TB and MDR-TB patients across the Western Province.[214] Mabadauan Health Centre has capacity to treat five MDR-TB patients at

any one time, but the literature available does not report similar arrangements in other remote communities in the Western Province. McBryde[109] found that 34.2% of cases on Daru have MDR-TB and that the provincial burden is likely to be much higher.

To alleviate some of the pressure of high volumes of referred patients arriving on the already densely populated Daru Island, the Torres and Cape TB Control Unit have an agreement with the Western Province Health Authority that if the patient is not in a critical condition, then laboratory confirmation is required prior to referring patients suspected of having pulmonary TB to DGH.

Queensland Health facilities in the TSPZ also see a high proportion of clinically diagnosed extrapulmonary cases in adults and in children. A recent study conducted in the Balimo region in the Middle Fly district of PNG reported 75% of TB cases as extrapulmonary.[214] Limited availability of diagnostics was cited as a contributing factor as well as overestimations that can occur when a clinical diagnosis is symptom-based.[214] Diagnostic tools for extrapulmonary TB such as CT, MRI or pleural fluid taps are not available on islands of the TSPZ however, if there is a visiting doctor who can perform fine needle aspiration on enlarged lymph nodes in children, then these are sent to the Queensland Mycobacterium Reference Laboratory in Brisbane for analysis. Regardless of diagnostics available, all non-critical extrapulmonary TB cases are referred to DGH for further examination. Children are referred immediately as symptoms are indicative of recent *Mycobacterium tuberculosis* transmission and there is a high risk of disease progression post-exposure.[215]

It is a fairly frequent occurrence for referred patients from PNG Treaty villages to refuse to travel to Daru due to financial and other constraints. Patients and escorts without family on Daru may be subject to food and housing insecurity due to inability to pay and may fear physical and sexual violence on the small island.[216] There is also no financial assistance to cover patient transport and the cost to get to Daru from the Treaty villages closest to Australia is between $180-240.[110] At least one patient has died as a result of their inability to afford fuel.[10]

1.20.1 Medical Evacuation

When patients are in a critical condition and clinicians are unsure if safe and ethical transfer back to PNG can be accomplished, efforts are undertaken to medically evacuate patients via helicopter to Thursday Island Hospital in Queensland; a 45-minute flight from the border. The

decision to medically evacuate patients to an Australian facility or to refer to DGH can have devastating consequences for the patient, and is a heavy weight to bear for the Australian-based physician. Medical evacuations (medivacs) depend on patient acuity and availability of isolation rooms for patients suspected of having pulmonary TB at Thursday Island Hospital and further afield at Cairns and Townsville hospitals. Generally, if the patient is not in a critical condition, a referral is made to DGH.

The Commonwealth Department of Health provides Queensland Health with funding via National Partnership Agreements for medivacs and treatment costs for PNG nationals accessing health facilities via the TSPZ.[217] A requirement of the funding allocation is that the PNG patient must have entered Australia via the TSPZ and not via any other designated air or sea port (i.e. Cairns Airport).[217] **The cost to medivac PNG national TB patients is currently unknown** (this is addressed in Chapter 5), however given expenses attributed to aeromedical retrieval from remote settings and the frequency with which patients with a range of health issues are evacuated, it is not unreasonable to suggest that the funding likely falls short of actual costs incurred. Further investigation is required to inform any future funding model.

Implementation of the *Management of PNG traditional inhabitants presenting to Queensland Health facilities within the Australian islands of the Torres Strait Protected Zone* Policy (henceforth referred to as the Policy) aimed to assist clinicians to make decisions regarding eligibility for medivac. According to the Policy, all PNG nationals presenting to PHCs in the TSPZ are triaged, with minor conditions treated, chronic conditions referred back to the PNG health service and patients in critical conditions managed according to their acuity.[218] Reductions of numbers of medivacs were observed in 2019 however, one cannot see this as an accurate measure of financial savings or success without also looking at patient outcome indicators.

Decisions to medivac PNG nationals appear to be partly explained by patient acuity and partly explained by decision-maker characteristics. Physicians at Thursday Island Hospital are rostered on-call to undertake medical consults for patients presenting at outer island PHCs, but medivac decisions are mostly allocated to doctors with higher authority. Staff turnover and promotion both lead to changes in the authoritative figures, and the threshold for determining patient acuity that warrants medivac can change with it. There are anecdotal reports of increased (or decreased) numbers of medivacs of PNG national patients being associated with

specific personnel. There are also times when inclement weather, aircraft maintenance or bed shortages prevents medical evacuations.

On most occasions, patients from PNG seeking healthcare in Australia are reliant on a physician's ability to diagnose, develop differential diagnoses and determine treatment or management options within an environment that does not permit patients to be recalled across the border for further assessment. Other than the obvious ethical and moral dilemmas that this rule conjures (detailed in Chapter 5), there are two main clinical implications. The first is that physicians who may have no experience in the management of TB are now expected to use their clinical judgment to care for a patient with no possibility of follow-up. Secondly, decisions made with limited information may not result in optimal patient outcomes and both these scenarios could lead to decisions that lead to loss of life. Until this thesis, the auditing and follow-up of the outcomes of decisions in this situation has been minimal.

There are critical gaps in understanding clinical judgment of physicians in the Torres Strait / PNG border region and the unquantifiable measure of accountability. Firstly, there is the unknown association between clinical judgment and how socio-demographic characteristics of the patient affect decisions as has been observed in other settings.[219] A difference in background or experience in this context may lead to different decision-making processes affecting the perceived threshold of patient acuity that triggers a medivac decision.

There are also issues of patients not always having the opportunity to meet a doctor face-to-face or via telehealth. Decisions about care are frequently discussed directly with outer island nursing staff over the telephone instead of a via a visual medium such as telehealth services which further compounds the difficulty of clinical decision making. This then has the potential to affect care and outcomes for patients who are not necessarily aware of how clinical decisions are made, how said decisions may affect their care and health outcomes or if they have a recourse to question the medical decisions made about their care.

The Policy states that ethical referral back to the PNG health system requires 'no reasonably foreseeable risk of clinical deterioration following the provision of care' and without regular, reliable transportation for patients, it can be difficult for SMOs to adhere to the policy. From 2017-2018, the average number of days patients waited in the Treaty villages for transportation to Daru was 120 days (D. Peniyamina, personal communication, 2018). As the SMO's involvement typically ends at the time of consultation, they are not always aware that there are

transportation delays, at which point the patient may have already left the clinic. On occasions that SMOs are aware of transportation delays, it is reasonable to ask whether discharge without reassessment which factors in delays for patients accessing further care is ethically, morally or even clinically sound.[57]

Not all clinical presentations are emergencies and some patients can deteriorate after having been stabilised. The Policy states that if a CEWT, MEWT or Q-ADDS score is 5 or more, medivac criteria has been met, however the scoring tool is limited in scope and does not allocate points for metabolic decline or malnutrition. Further, if a patient presents with pyrexia and is administered paracetamol to reduce the fever, the CEWT / MEWT / Q-ADDS score can be reduced. If a fever is the difference between a CEWT / MEWT / Q-ADDS score of 4 or 5 and the patient is discharged post-paracetamol, adherence to Policy has been achieved. The inherent problem with this is that the underlying condition may not have been addressed and the patient may remain at-risk of deterioration. **The level of adherence to the Policy, of following the path of medivacs for patients with elevated deterioration detection scores is unknown.** This is addressed in Chapter 5. **Further, outcomes of patients referred back to the PNG health system is largely unknown.** This is addressed in Chapters 4 and 5.

If a PNG national dies in the TSPZ or shortly after discharge from a Queensland Health facility, the coroner is rarely involved and autopsy can be considered culturally inappropriate by some families. The case might be reviewed in a local Morbidity and Mortality meeting, otherwise, there is minimal transparency in cross-border decisions and limited support for the SMO that made the life-or-death decision.

1.21 Importance of the Proposed Research

TB has been adversely affecting Indigenous Australians in Northern Australia, predominantly for the past century and while inroads have been made to reduce the burden of disease, vigilance is required to continue the downward trend. This is particularly important in areas where there are international air and seaports, and where there is established and ongoing TB transmission such as at the open border between the Torres Strait in FNQ, Australia and PNG. Although recrudescence of TB transmission in the broader Australian population is unlikely[220] due to improved living standards, public health legislation, state and national TB programs, BCG vaccination and effective treatment,[221] efforts to halt transmission must continue, especially in more vulnerable populations such as the Northern Australian Indigenous

population. One quarter of the world's population is currently infected,[222] and as *tubercle bacillus* is a most persistent organism, it can and will re-establish itself if given the chance.[220]

To date, strategies within the Global Plan to End TB in Indigenous peoples have not been fully realised in Northern Australia. At a state level, Queensland has identified its Indigenous population as high risk but other components of the End TB targets could be improved, such as improving access; improving case finding methods; reporting using disaggregated data by key population, and ensuring community consultation which involves designing programs that recognise sociocultural barriers and incorporates grassroots solutions.[3]

There is no doubt that TB Control in the Torres Strait / PNG region is compounded by many factors under the themes identified in other challenging environments described in Chapter 1, part 1. Relevant to this region, themes include overcrowding, poor nutrition, personal financial constraints, health illiteracy, treatment delay, comorbidities, climatic challenges, geographic challenges, limited human resources, treatment interruptions, disrupted health services, access issues, allocation of financial resources and cross-border. Additional themes identified in this particular context include limited laboratory support, clinician education and policy implications in remote settings (Table 1.1.2).

Table 1.1.2 Themes identified in Chapter 1, Part 1 - TB and Global Challenges – Managing tuberculosis under challenging circumstances: a scoping review - as they relate to TB control in the Torres Strait / PNG border region

Individual risk themes	Programmatic challenge themes	Other themes identified in cross-border literature
Overcrowding	Climatic challenges	Limited laboratory support in remote settings
Poor nutrition	Geographic challenges	Clinician education
Personal financial constraints	Damaged health infrastructure	Policy implications
Health illiteracy	Limited human resources	
Treatment delay	Insecurity	
Comorbidities	Treatment interruptions	
	Disrupted health services	
	Access issues	
	Allocation of financial resources	
	Cross-border management/control of TB	

While there is evidence that primary transmission of TB is occurring in FNQ, little is known about the epidemiological risk profile of the Torres Strait / PNG border region. Knowledge gaps in the region are many and while significant data collection has been undertaken to form the basis of this thesis and will be made available for future research, addressing the knowledge gaps will require a concerted effort by many scholars.

In recognition of the breadth of knowledge gaps related to TB control in the Torres Strait / PNG region, careful deliberation has been undertaken to determine what evidence is needed to make grassroots improvements at a programmatic level in the Torres Strait. As I am both the researcher and the Nursing Director of the Torres and Cape TB Control Unit in the Torres Strait, I find myself in the unique position to be able to use and synthesize evidence in this thesis to identify and characterise the reality of TB management challenges in the region and change policy. In acknowledging that this research was driven by translational motivation, integrating new evidence into primary healthcare services will enable the Torres and Cape HHS to address deficits and support point-of-care diagnostics and clinical decisions. By positioning

the research in this real-world context, the evidence derived from this research can be used to inform changes and support programmatic or policy design to improve patient outcomes.

Figure 1.2.23 Murray Island, Torres Strait (Foster, 2017).

This chapter has demonstrated that many of the themes identified in Chapter 1, part 1 – TB and Global Challenges - Managing TB under challenging circumstances: a scoping review (lessons from international settings), are relevant in the Torres Strait / PNG border region. Given the large numbers of gaps identified in this chapter, research problems have been selected based on the themes as they apply to the management of TB at the Torres Strait / PNG border that have sufficient likelihood of generating evidence to lead to policy improvements. Research problems, themes as they apply to the Torres Strait / PNG border region, research questions, hypothesis, and aims of chapters containing studies in this thesis are as follows:

Chapter 3 - Diagnostic Yield

Research Problem: Collecting three sputum specimens for the diagnosis of PTB is expensive and time consuming and may lead to diagnostic and treatment delay.

Theme/s: Limited laboratory support in remote settings; clinician education; climatic challenges; geographic challenges; disrupted health services; cross-border management/control of TB; policy implications

Research Questions:

1. What is the diagnostic yield of two and three sputum specimens collected in the Torres Strait Islands?
2. What is the impact of collection modality, clinician involvement in specimen management and quality of specimens on diagnostic yield?

Hypothesis: The diagnostic yield of two sputum specimens is sufficient for the diagnosis of pulmonary TB in the Torres Strait / PNG border region

Aims:

1. Determine the diagnostic yield of sputum specimens collected in the Torres Strait Islands for pulmonary TB (PTB).
2. Examine sputum smear negative diagnoses among patients diagnosed with PTB in the Torres Strait.
3. Examine the quality, collection and transportation of specimens from remote settings in the Torres Strait Islands and assess how these factors affect diagnostic yield.

Chapter 4 - The Rise of Drug-Resistance

Research Problem: Cross-border transmission of DR-TB is an established risk. To improve outcomes for patients, an understanding of the epidemiological profile of affected patients is required.

Theme/s: Overcrowding; poor nutrition; personal financial constraints; health illiteracy; treatment delay; comorbidities; geographic challenges; treatment interruptions; disrupted health services; access issues; cross-border management/control of TB; limited laboratory support in remote settings; clinician education; policy implications

Research Questions:

1. What are the characteristics of patients with DR-TB?

2. What is the geographical distribution of DR-TB in the Torres Strait / PNG border region over two decades?
3. Are patients diagnosed with DR-TB impacted delays in effective treatment commencement?
4. Are there predictors of treatment outcomes for patients diagnosed with DR-TB?

Aims:

1. Characterise patients diagnosed with DR-TB in the Torres-Strait between 2000 and 2020.
2. Identify the factors contributing to mono and MDR-TB as diagnosed in the Torres Strait between 2000 and 2020.
3. Map the geospatial distribution showing DR-TB in the Torres Strait between 2000 and 2020.
4. Identify the time from onset of symptoms to treatment commencement in Torres Strait / PNG patients with presumptive TB between 2000 and 2020 and identify variables that may have contributed to diagnostic and treatment delays.
5. Identify factors that contribute to unfavourable outcomes in patients with DR-TB.

Chapter 5 – High Price

Research Problems:

a) The Australian Government funding model for the management of TB in PNG Nationals requiring aeromedical retrieval and medical management should be evidence-based. However, currently, the true cost of managing these patients is unknown. Adequate allocation of funds requires evidence of cost.

b) Currently, frontline clinicians use deterioration detection scores and local policy to determine if PNG national patients with presumed TB in need of critical care qualify for aeromedical retrieval to an Australian hospital. However, it is unknown how these tools designed to support the clinicians' decisions affect outcomes for these patients.

Theme/s: Treatment delay; geographic challenges; access issues; allocation of financial resources; cross-border management/control of TB

Research Questions:

1. What is the cost to medically evacuate and manage one PNG patient diagnosed with TB who entered Australia via the TSPZ?
2. Is funding provided to Queensland Health by the Commonwealth of Australia sufficient to medically manage all PNG patients requiring aeromedical retrieval and medical management?
3. How is local policy on TB management met when managing PNG patients presenting to health facilities with presumptive TB in the TSPZ?

Aims:

1. Identify the cost of aeromedical retrieval and medical management of an exemplary TB patient from PNG into the Australian health care system.
2. Identify the median length of stay in the Australian health care system for PNG nationals who have been diagnosed with TB and medically evacuated from the TSPZ between 2016 and 2019.
3. Explore adherence to local policy in relation to managing PNG patients with presumed TB presenting at health facilities in the TSPZ between 2016 and 2019.
4. Assess the impact of clinical deterioration detection scores and their useability in effectively managing PNG patients with presumed TB presenting at health facilities in the TSPZ between 2016 and 2019.

Chapter 6 - Paediatric TB

Research Problem: Rapid diagnosis of TB in children is critical to reduce TB-related mortality. Chapter 5 identified a need for a Child Early Warning Tool to both identify TB disease in general and rapidly detect severe TB disease in children presenting to health facilities in the TSPZ.

Theme/s: Poor nutrition; health illiteracy; comorbidities; geographic challenges; treatment interruptions; access issues; allocation of financial resources; cross-border management/control of TB; limited laboratory support in remote settings; clinician education; policy implications

Research Questions:

1. Are there population-specific indicators associated with PNG paediatric patients with presumptive TB presenting to clinics in the TSPZ?
2. Can existing paediatric TB diagnostic approaches used in the Torres Strait be enhanced by diagnostic approaches used in other settings?

Aims:

1. Review all presumptive and diagnosed TB cases in the PNG paediatric population who presented to health facilities in the TSPZ between 2016 and 2019.
2. Compare current local practice and available diagnostic algorithms to support diagnostic and care decisions for paediatric patients from PNG who present to health facilities in the TSPZ with signs and symptoms of TB between 2016 and 2019.
3. Examine outcomes in paediatric patients that presented with signs and symptoms of TB to the TSPZ between 2016 and 2019.

While TB is a curable and treatable disease, significant socioeconomic and political obstacles remain to eliminating the incidence of TB and MDR-TB, and to Closing the Gap between Indigenous and non-Indigenous Australians. These barriers are especially pronounced in the difficult circumstances discussed herein, and future TB control programmes should be designed based on the evidence of effective past approaches, learning from the less successful ones, and planning for the long-term elimination of TB.

1.22 References

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the Australian Islands of the Torres Strait Protected Zone, presumed to have or diagnosed with tuberculosis (Appendix 3). Cairns, Queensland: TCHHS.

156. TCHHS. Appendix J5 *TB Screening – PNG national patients requiring Medivac algorithm.* In Appendix J2 Procedure: Management of Papua New Guinea Nationals accessing healthcare within the Australian Islands of the Torres Strait Protected Zone, presumed to have or diagnosed with tuberculosis (Appendix 2). Cairns, Queensland: TCHHS.

157. TCHHS. Appendix J8 *Clinical Management of Papua New Guinea traditional inhabitants presenting to TCHHS facilities flowchart*. In Appendix J7 Procedure: Papua New Guinea traditional inhabitants presenting to Queensland Health facilities within the Australian Islands of the Torres Strait Protected Zone (Appendix 1). Cairns, Queensland: TCHHS.

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Figure 2.1 Thursday Island Hospital (Foster, 2017).

Chapter 2: Data collection: a tale of boats, cockroaches, and medical records

Aims:

1. Describe the history of electronic medical records systems used in the Torres Strait.
2. Provide an overview of the Torres Strait / Papua New Guinea cross border data integrity project.
3. Provide detailed explanations of data sources used within the PhD thesis.

In this descriptive chapter, I provide a background to historical and current medical record data collection methods for Papua New Guinea (PNG) nationals who have presented to health facilities in the Torres Strait. I also explain all data sources used during the PhD for residents of the Torres Strait Islands diagnosed with tuberculosis (TB) and PNG nationals accessing health services in the Torres Strait Protected Zone (TSPZ). The data collection project and processes described herein may contribute to future healthcare research in the Torres Strait in the following ways: 1) future researchers will have access to data related to diseases of public health significance in PNG nationals who have accessed health facilities in the Torres Strait; 2) future researchers will be able to perform specific disease-related searches in electronic records and 3) future researchers will have access to four comprehensive, consolidated and accurate aggregate datasets available for TB patients who were diagnosed in the Torres Strait between 2000 and 2020. In addition to data linkage of all relevant variables for TB cases, additional data linkage was performed for all presumptive TB cases that presented to Torres and Cape Hospital and Health Service (TCHHS) Primary Healthcare Centres (PHCs) between 2016 and 2019.

2.1 Contribution

My contributions to data collection were as follows:

- I submitted a business proposal and obtained State and Federal-level approval to undertake a data integrity project to gather all historical medical records of PNG

nationals stored in the Torres Strait, and to transfer them into a secure electronic medical records system.

- I managed the cross-border data integrity project and designed the naming convention used within the available electronic medical records system.
- My collaboration with the Patient Safety Quality Director of TCHHS, led to the mandating that PNG national medical records be stored electronically.
- I obtained Ethics approval from the Far North Queensland Human Research Ethics Committee (HREC/17/QCH/74-1157), the Chair of James Cook University Human Research Ethics Committee (H7380) and obtained Site-Specific Authorisation via data custodians in the TCHHS and the Research Governance Officer.
- I obtained Public Health Act authorisation (QCH/36155 – 1157).
- I was the lead author of this chapter and shared drafts with my supervisory team.
- I collected, cleaned, collated and analysed all data used in this PhD using sources described herein: in IBM SPSS Statistics, versions 24-27 (2017-2021), Armonk, New York, United States or Excel (2016, North Ryde, Australia).

2.2 Introduction

Health data must be gathered and examined to understand and improve service delivery to PNG nationals accessing Australian PHC services for TB diagnosis and management in the TSPZ cross- border region. In the early 1990's Holt's database became the first electronic medical records system used in the Torres Strait.[1] It was implemented to consolidate handwritten patient notes.[1] A recall system and chronic disease database called FERRET which required manual insertion of data and is still used in some communities, complemented this database.[1]

In 2011, Holt's database was phased out and replaced with Best Practice.[1] Best Practice is an electronic patient information system used for all patients who present to PHCs and the Thursday Island Hospital Emergency Department in the Torres Strait. Best Practice has an embedded recall system and is used to record details of all patient presentations, observations, medical consultation notes, medical history, chronic disease management, investigations, health checks, immunisations, medication management, screening, and all medical/clinical interventions. Best Practice was designed to be used in general practitioner settings, but it has some limitations when managing patients with infectious diseases. Mainly, its coding, case management and contact tracing and screening mechanisms are not conducive to the safe

management of patients with active or latent TB. However, as the most reliable open access data source of medical information across all health facilities in the Torres Strait, its use by all clinicians in the region remains critical.

The systematic entry of PNG national medical records was not performed during the implementation or subsequent use of Holt's database. Furthermore, it was not part of the data migration plan to roll out Best Practice in the region. Consistent and secure storage of PNG national's medical records was not available for patients accessing PHCs in the Torres Strait until 2014.

2.3 Cross Border Data Integrity Project

In 2014, I was working as the tuberculosis (TB) Clinical Nurse Consultant for the Queensland Department of Health Communicable Diseases Unit in Brisbane, where approximately 60% of my workload was related to TB in the Torres Strait. I was seconded to the TCHHS to work on a Federally-funded cross-border TB project. This project aimed to support the transition of TB treatment for PNG nationals from Queensland Health's PHCs in the TSPZ, to the PNG health system.[2]

The bilateral Cross Border Health Issues Committee is co-Chaired by the Australian Government Department of Health and PNG Health. After consulting with members, I implemented some initiatives, including providing TB education for residents of the Torres Strait and PNG Treaty villages that lie adjacent to the Torres Strait, the development of a TB animation[3] in local Torres Strait Creole and the development and piloting of TB recognition and diagnostic procedures for clinicians working in PHCs in the TSPZ.[4] However, the migration of PNG-related patient health data into Best Practice, proved to be the largest and most challenging initiative.

I led a team from 2014 to 2016 that oversaw the collection, centralisation and scanning of historical paper-based records, which were entered into Best Practice. Prior to 2014, only handwritten patient notes were available for residents of PNG who had accessed health facilities located in the Torres Strait. Decades worth of hardcopy PNG patient files or loose sheets of paper were scattered throughout the Torres Strait Islands, with the earliest found dating back to 1953. Some were carefully arranged in large double-holed binders and neatly stacked on the shelves of PHCs in alphabetical order or numerically by unique record numbers

(URN). A URN is a unique identifier that is allocated per patient and is used to match patients with their clinical records.[5] Others were kept in dusty boxes in sheds or storage rooms, stored in rusty or broken filing cabinets, wrapped in faded tarpaulins and kept in the backyard of a PHC where they became weathered, dirty, dusty, mouldy and damp from exposure to the harsh tropical climate (Figures 2.1.1 and 2.1.2). My team and I uncovered thousands of patient files, and we sifted through them from 2014 to 2016. A common feature of the files was the faeces of cockroaches and rats, or so I was told.

Figure 2.1.1 PNG national patient records stored in the backyard of a Primary Health Centre (Foster, 2015).

Figure 2.1.2 Rust-covered PNG national records at a Primary Health Centre (Foster, 2015).

During the data collection process, I travelled by fixed-wing aircraft or helicopter to each PHC located in the Torres Strait Islands. At each PHC, I located and boxed up all PNG patient files. Since I needed to move the files from the TSPZ to the Torres Strait Permanent Biosecurity Monitoring Zone, I was required to surrender all patient files to the designated biosecurity officer stationed on each island.[6] To maintain the confidentiality of the files, I was present when the biosecurity officer inspected the files to ensure they were free from material that may pose a biosecurity threat. In most instances, the medical files were sprayed to neutralise dead insects and their products.

Thereafter, the boxes of files were placed on a barge for transport to Thursday Island Hospital. Boxes of files were stored in a condemned building on the Thursday Island Hospital campus, as space was at a premium. All PNG patient files contained in Thursday Island Hospital were also included in this project. The files contained clinical information for patients who had been medically evacuated from the outer islands and entered into the tertiary Australian health care system. Despite the poor condition of some of these records, the Cross Border Data Integrity Project team successfully salvaged, coded and entered large amounts of data into Best Practice.

In just over two-years, my team systematically extracted and scanned complete patient files for any patient whose paper record contained any information pertaining to a communicable disease-related event of public health significance. This would lead to access for TCHHS clinicians to previously inaccessible data that had epidemiological significance on a broad scale. Due to limited funding, time constraints, and the sheer volume of patient records, only files containing evidence of investigations into or diagnoses of communicable diseases that are listed on Queensland's Health's Notifiable Conditions System (NoCS) were scanned into Best Practice (Appendix J1). This still meant, however, that my team were required to read all patient notes, that described hundreds of snake bites, falls from coconut trees, injuries from coconuts falling on patient's heads, tooth pain, injuries from domestic violence etc.

During the project, my Cross Border Data Integrity Project team collectively reviewed over 5,000 individual patient records and more than 30,000 individual pieces of paper. In 2016, a mandate was issued to enter all PNG national records into Best Practice across TCHHS. This mandate was written into *Policy 0090 - Papua New Guinea traditional inhabitants presenting to Queensland Health facilities within the Australian Islands of the Torres Strait Protected Zone.*[7]

2.3.1 Cross Border Data Integrity Project Team and Responsibilities (Figure 2.1.3)

The Cross Border Data Integrity project team comprised of an administration officer and two Registered Nurses at any given time. Three administration officers and five nurses were employed over the course of the project.

I trained Registered Nurses involved in the data integrity project in how to identify both presumed TB cases (known as suspected TB at the time of the project) and valid TB cases. I also trained nurses in using Queensland Health's laboratory system database called AUSLAB to identify supplementary diagnostic results. Registered Nurses were employed to read every page of the patient's file and manually enter keywords pertaining to a TB investigation or diagnosis into Best Practice, according to a naming convention.

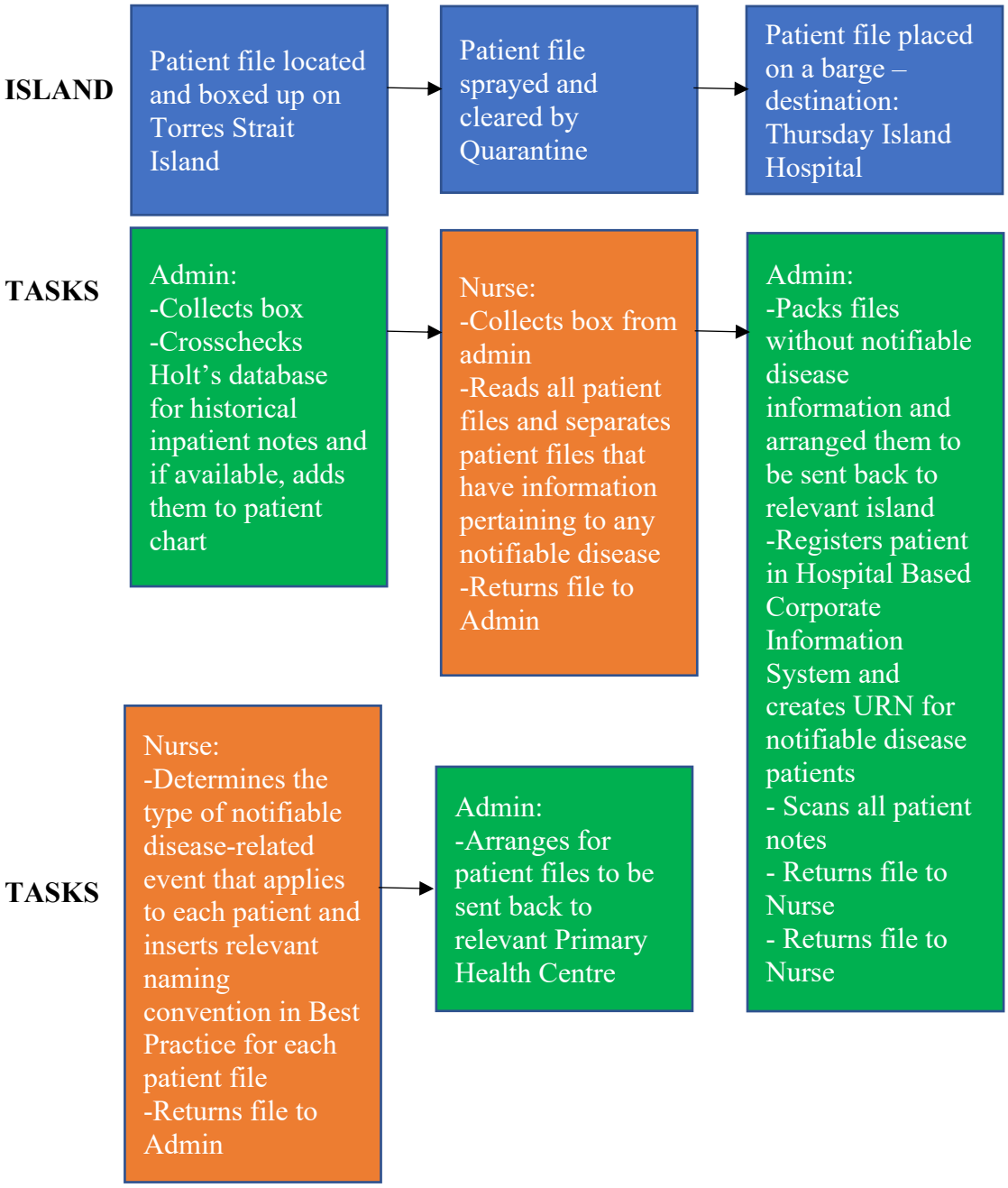


Figure 2.1.3 Process of collection and migration of PNG patient medical records into Best Practice during the Cross Border Data Integrity project.

2.3.2 Naming Convention

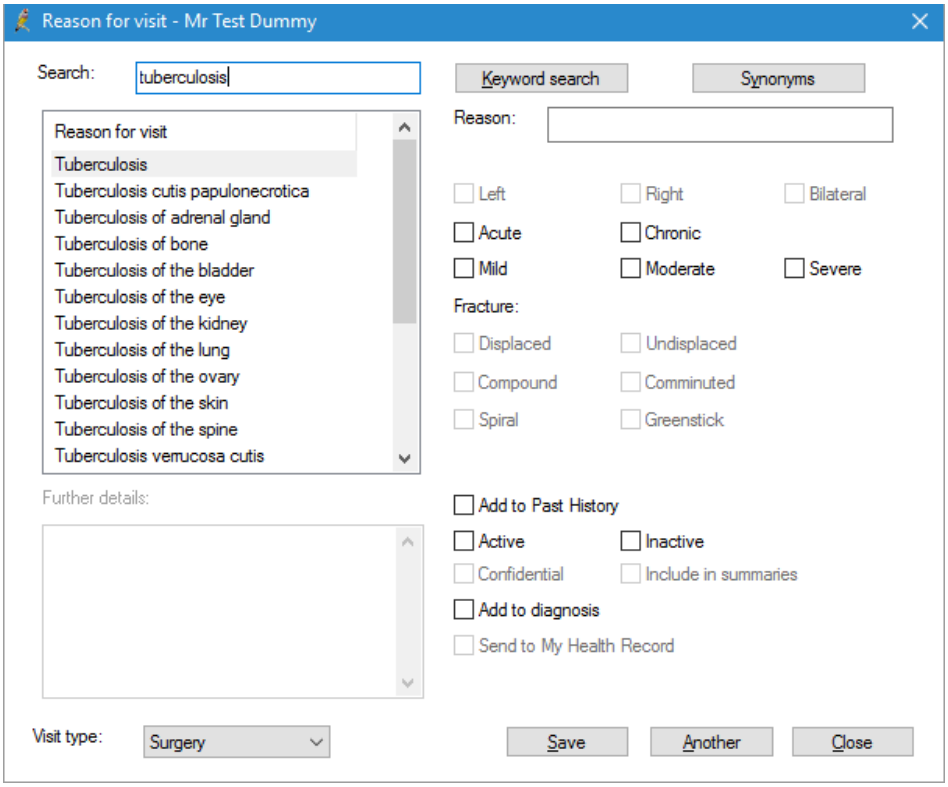
A naming convention was applied at the commencement of the project (Table 2.1.1). However, limitations of scanned medical records were presented. For example, staff and researchers could not extract information based on keywords - scanned files in electronic databases lack the availability of keyword searches. Furthermore, project staff were limited by insufficient options within Best Practice to adequately describe patient pathways in relation to TB (Figure

2.1.4). The only relevant pre-select option Best Practice allowed was the diagnosis of TB. The software did not have capacity to describe alternate patient pathways such as contact with a known TB case, being symptomatic for pulmonary TB or extrapulmonary TB, investigations of a potential TB case, a diagnosis of multi-drug resistant (MDR) TB or a previous TB diagnosis. Further, there was no way to track treatment or manage follow up of confirmed cases.

Table 2.1.1 Naming convention applied to TB-related data during the Cross Border Data Integrity Project

Code	Description
suspected tuberculosis	Where any of the following were ordered or mentioned in patient notes or where laboratory results were found on loose sheets of paper in the patient's file: Signs and symptoms of TB (cough, fever, weight loss, night sweats, haemoptysis, enlarged lymph nodes) or close contact with a known TB case Acid-fast bacilli, AFB, GeneXpert, GXP, Gen Ex, GenX, Xpert, sputum sample, smear sample, sputum smear, chest x-ray, CXR, tuberculosis, TB, or mycobacterial culture
tuberculosis screening for medivac	For any patient file that documented that a chest X-ray was ordered prior to the patient or the escort requiring aeromedical evacuation
contact screening tuberculosis	For any patient file that documented contact tracing or screening for TB
Tuberculosis	For any patient file that documented a TB diagnosis, or where there was evidence that medical consultation and treatment for TB (but not Latent TB) had occurred. This code was also used when there was evidence of laboratory confirmation of TB disease.
query MDR-TB	For any patient file that mentioned multidrug-resistant (MDR)-TB or rifampicin resistance. If MDR was laboratory-confirmed, then the code 'tuberculosis' was applied.

A



B

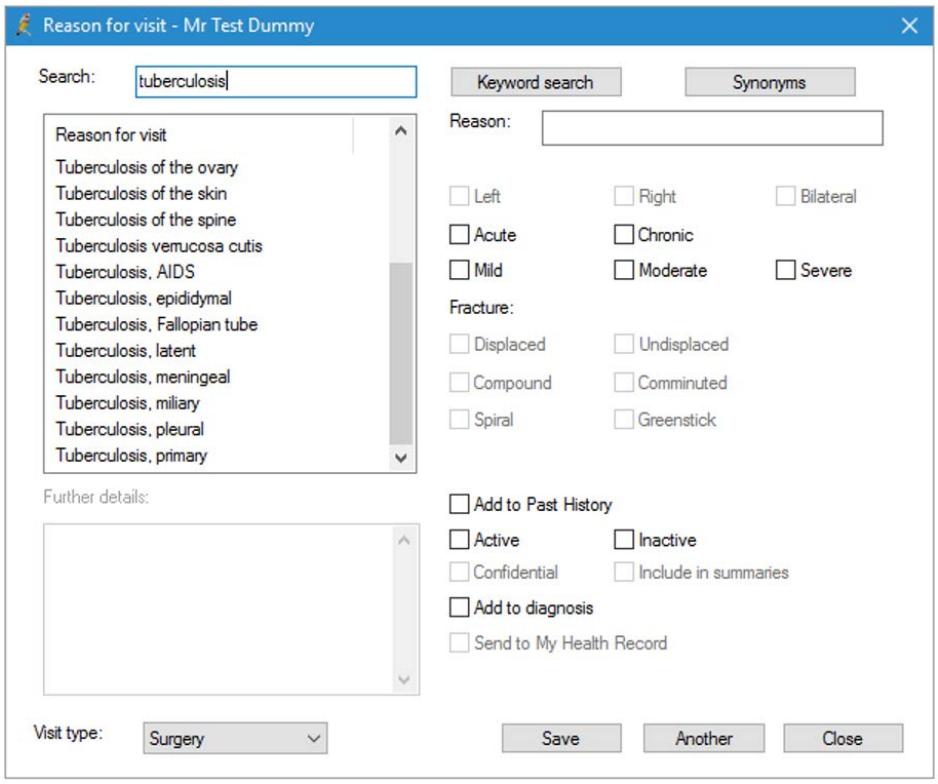


Figure 2.1.4 Screenshots depicting TB-related options available in Best Practice to document a TB-related presentation.

2.3.3 Challenges of the Cross Border Data Integrity Project

Although not directly involved in patient care, clinicians involved in the Cross Border Data Integrity Project had daily contact with large amounts of diverse clinical data. Due to the nature of the nurse's responsibilities, the nurses were required to engage with the data to extrapolate information pertaining to conditions of public health significance and investigate supplementary databases such as AUSLAB for laboratory results if further information was required to make a clinical judgement. Therefore, each encounter with patient data was purposeful; skimming was not conducive to accurate data mining.

As a result of exposure to vast amounts of personal and sometimes traumatic events in patient's medical files, the psychological effect that the project had on the team was profound. Counselling and support services were offered to staff members involved, as they were privy to sensitive information and stories of despair, desperation, starvation, domestic violence (including murder), abandoned children, excruciating pain, and in many cases, death. Further, team 'huddles' (informal team meetings) were encouraged to allow clinicians to speak freely with others on the team. There was a standing agreement in place that if a patient file was too difficult or traumatic to read, then the clinician could notify me, and I would work through the information and retrieve the data. I was not necessarily better equipped to deal with the potential psychological trauma of reading these health records; however, as the project lead, maintaining the mental health of project staff was of paramount importance. Anecdotally, to this day, some of the nurses the project employed can recount with accuracy some of the more devastating patient encounters they were exposed to.

Another challenge the project team and the wider clinician network in the Torres Strait faced was frequent, sometimes daily, interruptions and 'black-outs' of the Best Practice software. The Best Practice software is designed to support general practitioner clinics, which generally have a fairly small client and clinician base. Therefore, using it for a large and geographically dispersed health service tested its capabilities. The sheer volume of cross-border files being uploaded led to frequent system crashes, leading to negotiations with centralised software gatekeepers regarding how best to upload PNG files without interrupting day-to-day patient care.

The final challenge the team faced was discovering that many of the PHCs used outdated methods of storing PNG national records, which were insufficient and breached codes of

confidentiality.[8] Where possible, the Cross Border Data Integrity Project assisted a number of PHCs in consolidating, re-packaging and assigning URNs to their PNG national patient files. Duplicate files were commonly found and the Cross Border Data Integrity team frequently submitted details to the Health Information Manager who investigated and merged files as required. Deceased patient files were sent to or kept on Thursday Island for the Medical Records team to forward to Cairns for archiving. Although Best Practice now contains all available PNG national patient information pertaining to issues of public health significance from the 1950s to the present day, comprehensive patient information cannot be located in this database alone.

2.4 Data Sources

This thesis involved accessing, manually linking and merging information about active TB cases diagnosed between January 2000 and March 2020 and presumptive TB case presentations between January 2016 and December 2019. In March 2020, the international border between Australia and PNG closed due to the COVID-19 pandemic, significantly limiting access for PNG nationals seeking cross-border healthcare. Hence, data collection ceased at the end of March 2020.

Seven independent data sources (Table 2.1.2) were used to create four separate datasets. These consolidated, accurate, and complete datasets are as follows:

a) All laboratory-confirmed pulmonary TB cases diagnosed in the Torres Strait between 2000 and 2020 where at least three sputum specimens were collected
b) All drug-resistant TB cases diagnosed in the Torres Strait between 2000 and 2020
c) All PNG national patients who entered Australia via the TSPZ and presented with presumptive and confirmed TB between 2016 and 2019
d) All PNG national paediatric patients (<15 years) who entered Australia via the TSPZ and presented with presumptive and confirmed TB between 2016 and 2019

Typically, Queensland Health's Data Linkage Unit can assist researchers by utilising specialised software to match names and dates of birth across different Queensland Health databases. However, assisted data linkage was not an option for this thesis; data had to be collected manually from all accessed databases.

The reason for manual data collection was that spelling of names and dates of birth vary considerably for PNG nationals, and the spelling of someone's name can vary from week to week. Tok Pisin is a spoken language rather than written, and illiteracy is commonplace in the Treaty and non-Treaty villages of PNG's Western Province. Many PNG nationals know their year of birth but not the date or month. Therefore, there are many default dates used in the Torres and Cape Hospital and Health Service, the most common ones being 01.01.YEAR or 01.07.YEAR. This, coupled with the ad hoc spelling of names and duplicate files, led to the necessity of a systematic approach to 'hand' search patient information in various databases. For example, a patient with the name 'Teresa Example', date of birth 01.01.1980 may present and then a few months later, present again as 'Theresa Example', date of birth 01.01.1980. Without identification cards, there is no way for clinicians to know that this is the same patient; hence, a new patient registration is created, leading to duplicate patient files.

Further, there were many instances of PNG patients' first and surnames being 'back to front', at least according to Australian standards. For example, a patient may identify themself as 'Smith Isaac', and depending on the health administrator or clinician, the patient may be registered in some databases as 'Smith Isaac' and in others as 'Isaac Smith'. This frequent occurrence led to additional difficulty in the data collection phases of this research, as both versions of the patient's name needed to be manually searched across all databases.

Table 2.1.2 The seven main independent data sources used for studies in this thesis

	Data Source	Data Custodian
1	Best Practice	Torres and Cape Hospital and Health Service
2	Notifiable Conditions System (NoCS)	Queensland Department of Health
3	AUSLAB Clinical and Scientific Information System	Pathology Queensland
4	The Viewer	Queensland Department of Health
5	Hospital Based Corporate Information System (HBCIS)	Torres and Cape Hospital and Health Service
6	Enterprise Picture Archiving and Communication System (PACS/XERO/MerlinVue)	Queensland Radiology Information System
7	Torres and Cape Remote Area Phthisis (TCRAP), including the PNG national presumptive and confirmed spreadsheets and data suite	Torres and Cape Hospital and Health Service

Comprehensive patient information cannot be located in one database alone. Thus, it was necessary to access all relevant data sources, as required, for each study within this thesis. As an example, when determining the presence of symptoms for the study in Chapter 3, I accessed Best Practice software and the TCRAP databases to determine whether patients were symptomatic upon presentation. However, in the early data collection stages of this study, I noticed that some symptoms were documented on imaging request forms. Thus, for the third and fourth studies in Chapter 4, I cross-checked all reported symptoms against Best Practice, TCRAP and PACS software. For patients that had been transferred to Cairns or Townsville Hospitals, I also cross-checked information on the Viewer.

2.5 Determining the 'Source of Truth'

As clinical information systems are only as good as the inputted data, determining the 'source of truth' was challenging. Initially I had surmised that HBCIS software (where initial patient registration and allocation of URNs occur, which feeds into other clinical software accessed) would be the source of truth for patient demographics, followed by NoCS for TB-specific data. However, because a substantial number of patient files were registered in HBCIS many years after the patient first presented, and were registered by staff not involved in patient care, the data was subject to coding errors. Therefore, scanned Best Practice patient charts were determined to be the source of truth in some instances.

One limitation of the version of NoCS accessed during this PhD research was that in many instances, the date of the notification was many months after the date of diagnosis. Hence, the information contained in NoCS was often incongruent with patient notes scanned into Best Practice. The mismatches were mostly related to the date of onset of symptoms, diagnosis, gender, risk factors, disease site and island or village of residence. In these cases, scanned Best Practice charts were considered the source of truth as they were real-time sources for data entered by clinicians. The benefit of entering patient data in real-time is that the risk of errors associated with recall, faded memory or post/paste-related issues are minimised.

Throughout the data cleaning process, some laboratory-based inconsistencies were identified in NoCS and AUSLAB. There were some TB cases that had been listed in NoCS as fully-susceptible but were drug-resistant in AUSLAB, and vice versa. There were some patients whose residential address had been linked to Cairns instead of the Torres Strait and other cases that were missing from NoCS altogether. Further, there were some laboratory-confirmed TB

cases reported in NoCS where nucleic acid amplification testing, culture confirmation or both were not supported in AUSLAB. It is possible that cases reported in NoCS were confirmed by a private laboratory however, as private laboratories are not available in the Torres Strait, these cases were removed from analyses.

During the data cleaning phases for each study in the thesis, any data irregularities and inconsistencies found were communicated directly to the Queensland Communicable Diseases Branch. However, the Queensland Communicable Diseases Branch decided not to update historical information in NoCS. Therefore, the most accurate data available for future researchers in relation to TB in the Torres Strait between 2000-2020 is that which was collated for this thesis.

2.5.1 Best Practice

The origins and purpose of Best Practice use in the Torres and Cape Hospital and Health Service, have been described earlier. Best Practice was the primary source of information for much of this thesis. Best Practice was accessed for main lines of enquiry regarding a patient's clinical presentation and medical history. Additionally, it provided supplemental information that would not have been available otherwise. Best Practice was used as the source of truth for determining a patient's village residency and name. It also assisted with ascertaining contact history with a known TB case. This software has the added benefit of providing access to current and historical scanned patient notes.

2.5.2 Notifiable Conditions System (NoCS)

Queensland Health's NoCS is a register used to record all notifiable conditions in Queensland. Reporting notifiable conditions is a legislated requirement outlined in the *National Health Security Act 2007* and the *Public Health Regulation 2018*.[9] NoCS assigns one identification number per notified TB case, not per person. This allows for the evaluation of patients with multiple diagnoses of TB as well as the identification of those who progressed from drug susceptible to drug-resistant TB.

Until 2018, TB notifications within NoCS were classified as confirmed (valid/laboratory-confirmed) or probable (clinical diagnosis) (Table 2.1.3).[10] In 2018, the Torres and Cape TB Control Unit were notified by the Queensland Communicable Diseases Branch that previous 'probable' case notifications reported in the region from 2016 were under review and may not

be recognised as cases. This was in response to a review undertaken by the Communicable Diseases Branch which identified an increase in clinically diagnosed TB cases observed in PNG nationals diagnosed in the Torres Strait between 2016 and 2018.[11] To enable consistency across the state of Queensland, all clinically diagnosed TB cases were reviewed against the surveillance case definition which required some evidence that the patient's clinical course was consistent with TB.[11] As PNG nationals diagnosed with TB in the Torres Strait are generally referred to the PNG health system and do not commence effective TB treatment in Australia, the criteria for a clinical TB case could not be met. This led to the removal of multiple clinical TB diagnoses in PNG nationals diagnosed in the Torres Strait Protected Zone from NoCS (2016, 7 cases; 2017, 12 cases; 2018, 10 cases; 2019, 4 cases).[11]

The 2018 review led to the TB Control Unit ceasing to notify the Communicable Diseases Branch of probable TB cases in PNG nationals, leading to a reduction in probable cases diagnosed by local TB Specialists. Therefore, it is possible that there should have been more probable TB notifications to the Queensland Communicable Diseases Branch in 2018 than what is available in NoCS. Further, the Torres and Cape TB Control Unit were advised that all future probable cases would be reviewed by Queensland Health's leading TB Specialist prior to being entered as either 'probable' or 'unsure' within NoCS. These changes within the Communicable Diseases Branch led to local changes to case definitions and referral pathways for PNG patients. It was decided at a local level that clinical cases would be segregated into two categories – probable and possible (Table 2.1.4) and that only the probable cases, in addition to laboratory-confirmed cases, would be referred to the PNG health system.

Table 2.1.3 Queensland tuberculosis case definitions [10]

Case	Definition
Confirmed case	'*Isolation of Mycobacterium tuberculosis complex (M. tuberculosis) by culture OR* *Detection of M. tuberculosis complex by nucleic acid amplification testing EXCEPT where this is likely to be due to previously treated or inactive disease'.*
Probable case	'*A clinician experienced in tuberculosis makes a clinical diagnosis of tuberculosis, including clinical follow-up assessment to ensure a consistent clinical course.'*

Table 2.1.4 Torres and Cape Tuberculosis Control Unit presumptive case definitions and clinical management

Case	Definition	Clinical Management
Probable TB	'*A clinician experienced in tuberculosis makes a clinical diagnosis of tuberculosis'*[10]	Resident of the Torres Strait – the patient is isolated until microbiological confirmation or clearance is achieved. Where microbiological confirmation is not achieved, experienced TB physicians may decide to commence treatment. All patients that commence treatment are notified to the Queensland Department of Health. PNG national – the patient (if not medically evacuated to an Australian hospital) is referred back to the PNG health system. Probable cases in PNG nationals are notified to the Queensland Department of Health, and the PNG health system is advised that the case has been notified.
Possible TB	*A clinician experienced in tuberculosis recognises that the patient has some signs and symptoms or has risk factors that may be associated with a TB diagnosis, however an alternate differential diagnosis is more likely.*	Patient is discharged from the Torres and Cape TB Control Unit and referred to a General Practitioner or local health care services for ongoing health needs.

The aforementioned changes to Communicable Disease Branch case definitions in the Torres Strait did not impact the first two datasets created for this thesis, as only laboratory-confirmed case data were included in the analyses. However, the third and fourth datasets used for this thesis contain case notification data that is 'probable' (Table 2.1.4) and 'confirmed' (Table 2.1.3). These datasets also include information on cases diagnosed in PNG as a result of first presenting to a health facility in the Torres Strait Islands with signs and symptoms of TB and

being referred by the Torres and Cape TB Control Unit to the PNG health system with 'probable TB'.

From January 2014, NoCS commenced reporting the date of diagnosis as the date the notification was received.[9] Prior to January 2014, the date of diagnosis was reported as the symptom onset date, or if that date was unavailable, the earliest specimen collection date or notification date was used.[9] For the purpose of this thesis, all data sources were thoroughly interrogated to produce four separate dates: 1. the date of onset of symptoms; 2. the date of presentation to a health facility as a result of symptoms, specimen/s collection date/s; 3. the date of diagnosis and 4. the date that effective treatment commenced.

In preparing the datasets used in this thesis, cleaning NoCS datasets involved managing, deciphering and sorting the address fields. The first task was to remove all TB cases involving patients who resided in areas declared to be outside the designated study area. However, in many instances, island and village names were spelled incorrectly or missing, with only street addresses available. As a resident of the Torres Strait who is familiar with each of the Torres Strait Islands and Treaty villages, I was able to accurately apply the correct island and village name to each patient based on the available residential address.

2.5.3 AUSLAB

Pathology Queensland provides a diagnostic pathology service. AUSLAB is the software used to convey results to clinicians.[12] TB-related specimens are sent through Pathology Queensland networks to the Queensland Mycobacterium Reference Laboratory based in Brisbane, Queensland. TB-related data contained in AUSLAB includes acid-fast bacilli, nucleic acid amplification testing and culture results from isolates that were phenotypically tested for resistance to all first-line drugs, including streptomycin.[13] Results for resistance to second-line drugs are only available for patients in which first-line resistance was detected.[13] Pathology request forms are also available in AUSLAB, as are details about the type of specimen collected (e.g., sputum), the diagnostic test performed, the date and time of specimens collection, 'no-tests' and the quality and quantity of specimens collected. Other data available in AUSLAB that were used in this research include blood-based tests including but not limited to human immunodeficiency virus (HIV) results.

2.5.4 The Viewer

The Viewer was designed as a way for clinicians to access all inpatient and outpatient information across all Queensland Hospital and Health Services.[14] However, the ability for clinicians to access the read-only application is limited to the software The Viewer is connected to. Software relevant to this thesis and linked to The Viewer includes the Hospital Based Corporate Information System, Enterprise PACS, AUSLAB, and some data pertaining to inter-hospital referrals, aeromedical transfer, and appointments.

2.5.5 Hospital Based Corporate Information System (HBCIS) and Unique Record Numbers (URN)

Used for both inpatients and outpatients, HBCIS software is considered across Queensland Health as the source of truth for patient demographic data and is where URNs are generated.[5] A URN cannot be reassigned or deleted. Any request for a laboratory test or radiographic image cannot be undertaken without a URN. In addition to basic demographic data (e.g., name, date of birth, address), HBCIS also contains a patient's Medicare number, private health insurance status, and dates of admission, discharge and outpatient attendance.[5] HBCIS is also used to track the location of a patient's medical records.

In this thesis, where patients had the same or a similar name and date of birth, HBCIS was cross-checked with patient files against patient demographics and health facility attendance dates. Reliability and use of HBCIS can be adversely affected when individual patients have more than one HBCIS file. Due to name or date of birth discrepancies as previously stated, patients attending PHCs in the Torres Strait frequently have three or more URNs.

2.5.6 Enterprise PACS, XERO and MerlinVue

Enterprise PACS is a radiology informatics software allowing clinicians to upload and view medical imaging and radiology reports.[15] Enterprise PACS (Agfa IMPAX 6AGFA) imaging is also available to be viewed on XERO (Agfa-GEVAERT), a user-friendly interface. For the purpose of this research, both Enterprise PACS and XERO software were used to view chest X-rays and other imaging relevant to the diagnosis of TB. However, at times, Enterprise PACS did not contain the patient's medical imaging. In these cases, XERO was used to source them. The Enterprise PACS interface permits easy searching of patients, but in many instances,

radiology reports were only available in XERO. Both applications were open and used during all searches pertaining to patients' medical imaging.

MerlinVue (Central Data Networks PTY. LTD. NSW 2500, Australia) serves the same purpose as Enterprise PACS and XERO as a portal to access medical imaging. In this thesis, MerlinVue was only available for patients who were medically evacuated from the Torres Strait to Cairns. Thus, this software was only accessed for this research when specific data points were missing. For example, when investigating signs and symptoms upon presentation for patients who had been cared for in the Australian tertiary public hospital system, all other relevant software was accessed in the first instance. If the information could not be located, then a search for medical imaging requests in MerlinVue, which often contained the reason for the request, including signs and symptoms of TB, would be performed.

2.5.7 Torres and Cape Remote Area Phthisis (TCRAP) Data Suite

As the Torres and Cape TB Control Unit do not have an electronic clinical information system specific to TB patient management, the TCRAP data suite was accessed during this research. The TCRAP data suite is a series of Queensland Health Excel spreadsheets, patient files, TB-related forms and information derived from patient charts (Figure 2.1.5). In addition to a range of clinical and demographic data and notifiable conditions report forms, patient folders also contain all correspondence about patients with the following health-related services or professionals: TB Physicians, General Practitioners, the Communicable Diseases Branch, the PNG Health System, the Cross Border Communication Officer, Daru General Hospital and Primary Health Centre staff. In addition, folders contain correspondence in which a cross-border medical alert is required, including with the Department of Foreign Affairs and Trade, Australian Border Force, and the relevant Torres Strait Island Regional Councillor.

Presumptive TB spreadsheets used for Australian and PNG residents contain clinical information and are used to track patients through various clinical pathways, follow up on pathology and radiology reports, record treatment and other outcome data and extract occasions of service data. Data is derived from clinician input on the Initial Visit form and there is a specific form assigned, depending on whether the patient is an Australian or PNG resident (Appendices J3 and J10).[16,17] The Initial Visit form details the signs and symptoms of TB which are cough >2 weeks and/or fever of unknown origin, night sweats, unexplained weight loss, haemoptysis and enlarged lymph nodes (>1cm, +/- discharging sinus). Questions related to TB-

specific risk factors are also included on the form. There is also space on Initial Visit form to collect the names and contact details of close contacts are collected for each patient with presumptive TB. The results are tracked within the relevant contact screening spreadsheet.

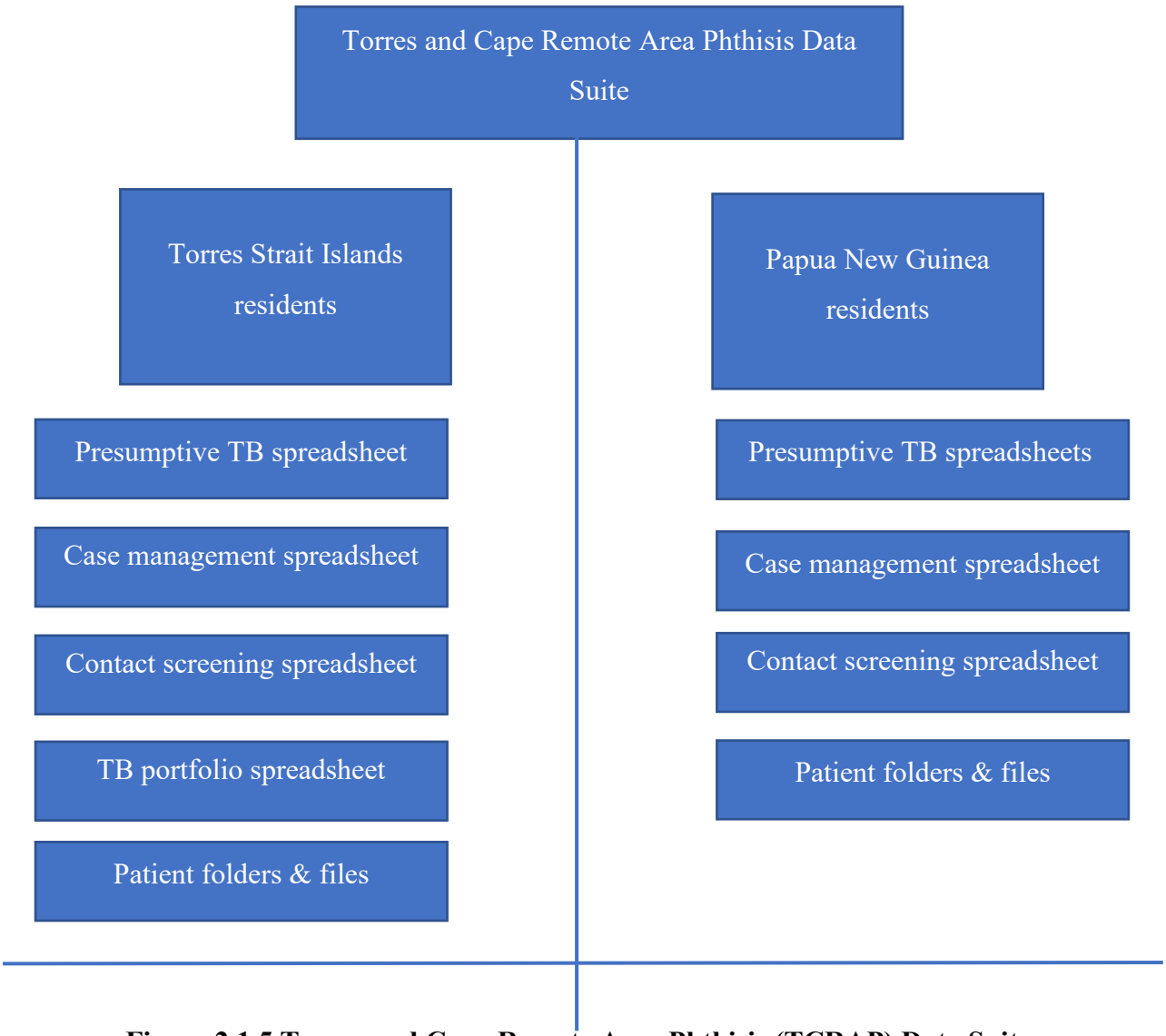


Figure 2.1.5 Torres and Cape Remote Area Phthisis (TCRAP) Data Suite.

2.6 Additional Data Sources

2.6.1 Aeromedical Retrieval and Disaster Management Branch (ARDMB) and Queensland Ambulance Service (QAS)

Written approval was obtained separately from the QAS Research in the QAS Torres and Cape York Local Ambulance Service Network (Appendix A8) and the Queensland ARDMB

Research Committee (Appendix A9). Descriptions of data provided and used are located in the first study of Chapter 5.

2.7 Data for Future Research

Four datasets were created for this thesis and variables used for each dataset are located in Appendix I3. These datasets can now be a source of information for other researchers with appropriate approvals. Sharing data collected during this thesis with future researchers must be balanced by authorised and appropriate measures that protect patient confidentiality. In the interest of privacy, confidentiality and security, Queensland Health restricts access to notifiable disease data.[18] At the completion of this thesis, the four aggregate datasets were archived into the 'Research Data James Cook University' repository.

2.8 References

Some Queensland Health and other Government agency documents may not be accessible to the general public.

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17. Torres and Cape Tuberculosis Control Unit. Appendix J10 *Initial Visit and Contact Tracing form used in the Torres and Cape Hospital and Health Service for residents of the Torres Strait and Cape communities.* Cairns, Queensland: TCHHS.
18. *Public Health Act 2005 s55*.

Figure 3.1 Mabuiag Island, which has the shortest runway in the Southern Hemisphere (Foster, 2014).

Chapter 3: Diagnostic yield

Overarching Aim #1: Investigate cross-border TB disease epidemiology.

Overarching Aim #2: Identify opportunities for evidence-based enhanced policy and practice for the management of TB in the region (Translational Research).

Aims:

1. Determine the diagnostic yield of sputum specimens collected in the Torres Strait Islands for pulmonary tuberculosis (PTB).
2. Examine smear negative status among patients diagnosed with PTB in the Torres Strait.
3. Examine the quality, collection modality and transportation of specimens from remote settings and assess how these factors affect diagnostic yield.

In this paper, I determine the diagnostic yield in patients with NAAT or culture confirmed drug-susceptible and drug-resistant PTB. I compare the collection of two and three sputum specimens for the diagnosis of pulmonary TB and the impact that collection modality and clinician management of specimens have on the quality and yield of specimens collected. Outputs of the analyses are that 1) two specimens are sufficient for the diagnosis of PTB in the Torres Strait / PNG border region; 2) there are high rates of smear negative PTB in the region; 3) nasopharyngeal aspiration can yield higher proportions of smear positive PTB diagnoses in paediatric patients aged <5 years via nasopharyngeal aspiration than with nasogastric aspiration; 4) higher than expected numbers of paediatric patients aged <10 years were diagnosed with culture-confirmed PTB via voluntary expectoration and 5) errors in labelling and transportation of sputum specimens in the tropics has little impact on diagnostic yield in patients with PTB.

3.1 Publication and outputs for Chapter 3

I was the lead author of the following peer-reviewed paper. My contribution to the study and subsequent outputs were as follows:

- I developed the concept for this study.

- I contributed to the design of this study.
- I wrote the ethics application for this study.
- I wrote the Public Health Act authorisation application for this study.
- I collected the data for this study.
- I attended a number of workshops about how to conduct quantitative research via the Doctoral Cohort Program at James Cook University (JCU).
- I used Excel and SPSS to organise the data collected and attended to all coding.
- I conducted the analysis with results reviewed by my supervisory team.
- I was the lead author of the manuscript which I initially drafted.
- I managed the submission of this manuscript which was peer-reviewed and accepted for publication.
- I prepared various presentations that included the results from this study for the Torres and Cape Hospital and Health Service Board – Safety & Quality Committee (29.04.21); Queensland Health Directors of Clinical Governance Implementation and Improvement Partnership (11.06.21) and the National Tuberculosis Advisory Committee (22.06.21).

3.2 Translation Research

- I met with all staff of the Torres and Cape Tuberculosis Control Unit and the Acting Executive Director Medical Services of the Torres and Cape Hospital and Health Service to discuss the findings of the study. I subsequently implemented a change to local procedure, whereby patients are now discharged from isolation after two negative acid-fast bacilli results have been received.
- I met with the Chief Scientist from Pathology Queensland on Thursday Island to discuss the findings of the study. I subsequently implemented a change to local procedure, whereby Pathology Queensland staff on Thursday now notify a nurse from the Torres and Cape Tuberculosis Control Unit when a sputum sample is received that has not been registered, labelled or packaged appropriately. This allows the Torres and Cape Tuberculosis Control Unit to proactively rectify the issue and ensure the sample is not rendered a ‘no-test’ and gets sent to the Queensland Mycobacterium Reference Laboratory for processing.

Results from this study are included in the following peer-reviewed publication.

Rural and Remote Health rrh.org.au
James Cook University ISSN 1445-6354

ORIGINAL RESEARCH

Tuberculosis in the Torres Strait: the lady doth test too much

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ABSTRACT:

Introduction: Smear-positive pulmonary tuberculosis (PTB) requires rapid diagnosis and treatment to prevent ongoing transmission. Collection of two sputum specimens is considered the minimum requirement for the diagnosis of PTB but current guidelines in the Torres Strait Islands, Australia, recommend three sputum specimens; this frequently delays treatment initiation.

Methods: A retrospective study was performed to ascertain the diagnostic yield of sputum specimens collected in the Torres Strait Islands. The study assessed demographics and characteristics of all PTB cases diagnosed between 2000 and 2018, and assessed the diagnostic yield in 143 patients from whom at least three sputum specimens had been collected prior to treatment commencement. Incremental and cumulative yield was calculated for each sputum specimen. Data were further analysed using binary logistic regression to examine the association between selected characteristics and a smear-positive acid-fast bacilli (AFB) result.

Results: Overall, AFB was detected from the first or second sputum specimen in 97 of 101 PTB cases that were sputum smear positive. A smear-positive result was more common (odds ratio 2.84, 95% confidence interval 1.08–7.46) for Papua New Guinea nationals compared to Australian born patients. Of the 429 samples collected, 76 (18%) were of poor quality and the association between poor quality specimens and smear-negative results was significant ($p<0.01$). Among sputum smear-negative cases, 5/42 (12%) had three consecutive poor quality specimens. The most common collection modality in adults was voluntary expectoration; done in 391/429 (91%) of all specimens collected. Alternative specimen collection methods were mainly used in children; induced sputum 1/429 (0.2%), gastric aspirate 26/429 (6%) and nasopharyngeal aspirate 7/429 (1.6%). Errors with labelling, packaging and transportation occurred in 44 specimens from 15 patients.

Conclusion: Two good quality specimens ensure adequate diagnostic yield for PTB and a third specimen should only be collected from patients with two negative specimens who have persistent symptoms. Ideally, decentralised Xpert Ultra® should be the frontline diagnostic test in remote settings, especially in settings like the Torres Strait Islands with high rates of drug-resistant TB.

Keywords:

diagnostic yield, sputum smear positive, tuberculosis, Torres Strait.

FULL ARTICLE:

Introduction

Pivotal to the control of tuberculosis (TB) is the ability for TB control programs to rapidly diagnose and treat the most infectious pulmonary TB (PTB) cases[1]. Until 2007, WHO recommended three sputum specimens should be collected for the diagnosis of PTB[2]. However, a large scale sputum microscopy analysis conducted in 42 high volume laboratories showed that the third specimen had a minimal contribution to case detection rates, with an incremental yield of only 0.7% to 7.2%[3]. A systematic review of 37 studies confirmed the high diagnostic yield for the first two specimens with a minor increase in sensitivity of 2–5% with collection of a third specimen[4]. Currently, WHO recommends a minimum of two sputum samples, which has the benefit of reduced time to diagnosis and treatment initiation with improved retention of patients in the care pathway[2].

In the Torres Strait Islands, Australia, standard practice still involves the collection of three early morning sputum samples or three samples over three consecutive days or three samples over 2 days using the 'spot-morning-spot' protocol, for local residents[5]. In Papua New Guinea (PNG), two samples are required, following the 'early morning-spot' protocol[6].

The Torres Strait Islands sit adjacent to the Western Province of PNG where TB is endemic and previous studies have demonstrated cross-border transmission of drug-susceptible and multidrug-resistant (MDR) TB[7]. TB diagnostic services (including specimen collection) have long been provided to PNG nationals permitted to travel to 14 Torres Strait communities in the Torres Strait Protected Zone (TSPZ) without passport or visa[8]. Primary health centres (PHCs) in the TSPZ are minimally staffed, with many one-nurse posts, and only two PHCs have X-ray facilities. TB diagnostic technology is not available in the Torres Strait and the distance from the northernmost Australian island in the TSPZ and the Queensland Mycobacterium Reference Laboratory in Brisbane, where testing occurs, is 2318 km away.

Aside from culture confirmation, TB is diagnosed using smear microscopy to detect acid-fast bacilli (AFB) in sputum by using DNA detection technology such as Xpert Ultra®, which can detect the presence of *Mycobacterium tuberculosis* and likely rifampicin resistance within 2 hours[9]. Rifampicin and isoniazid resistance constitute MDR-TB[9]. Xpert Ultra has greatly increased sensitivity compared to conventional sputum smear microscopy and its use in a decentralised fashion is now recognised as the preferred frontline test, especially in settings with high rates of MDR-TB[10,11].

The turnaround time for conventional microscopy from samples collected in the Torres Strait Islands ranges from a few days to a week and for culture is approximately 6 weeks. In remote settings, difficult cold storage and delayed transport lead to high rates of bacterial overgrowth, which may further delay reporting of results[12].

According to the Pathology Queensland laboratory information system, AUSLAB, a poor quality specimen (low volume, salivary contamination) for the diagnosis of *M. tuberculosis* is 'that which is less than what is required bacteriologically for diagnosis'. In Queensland, macroscopic evaluation of sputum is undertaken by a laboratory technician to determine good or poor quality and quantity of specimens for testing; however, few studies have

assessed the effect of sputum quality on the detection of *M. tuberculosis*[13]. Poor quality also refers to samples that are overgrown with contaminating organisms due to poor storage or dispatch delays, particularly in tropical climates[14]. Furthermore, adequate collection, documentation, packaging and transportation are arranged by clinicians and attention to detail is required to correctly match patients to specimens as well as ensure appropriate collection modalities are used[14].

The first aim of this study was to determine the diagnostic yield of sputum specimens collected in the remote Torres Strait Islands from Australian residents and PNG visitors. Collection modality, labelling and transportation of specimens in remote tropical locations were also examined for their effect on diagnostic yield. The second aim was to explore how improved decentralised diagnostic capability may assist earlier diagnosis and treatment initiation in remote settings. This international border, which allows free movement for designated traditional inhabitants without passport or visa, is a biosecurity risk[15]. Accessing health care is not a provision of the border agreement[15] and limited healthcare options for PNG visitors may lead to patients presenting late in their disease course, with advanced signs and symptoms of TB. Both a reduction in the number of sputum specimens required, and more rapid and decentralised diagnoses, have the potential to shorten the time to treatment initiation and increase retention of patients within the care pathway.

Methods

This is a retrospective study of all Australian residents who presented to a health facility in the Torres Strait Islands, and all PNG visitors who presented to a health facility within the TSPZ with clinical signs of TB, between 1 January 2000 and 31 December 2018. Patients were included if at least three specimens were collected within 2 weeks of each other, prior to commencement of treatment; and at least one specimen was positive for *M. tuberculosis* on culture or nucleic acid testing. Patients who had required medical evacuation to an Australian hospital outside of the Torres Strait Islands were excluded because collection modalities used in tertiary facilities are more advanced than those available in the Torres Strait Islands. A case was defined as smear-positive if one or more sputum samples tested positive for AFBs within 60 days of a positive Xpert *M. tuberculosis*/rifampicin (MTB/RIF) (Cepheid; https://www.cepheid.com/en/tests/Critical-Infectious-Diseases/Xpert-MTB-RIF) or *M. tuberculosis* culture. A case was defined as smear-negative if all three sputum samples were defined as negative for AFBs within 60 days of a culture positive result.

Data collection and management

A list of residents of the Torres Strait Islands and PNG visitors diagnosed with PTB within the Torres Strait and TSPZ respectively between 2000 and 2018 was obtained from Queensland Health's Notifiable Conditions System. All sputum smear results were extracted from AUSLAB and individually reviewed. Four cases were removed from the dataset as laboratory confirmation by Xpert or culture was not represented in AUSLAB. AUSLAB was also manually searched to retrieve data that had the potential to affect laboratory analysis and adversely affect diagnostic yield including sample quality, quantity and collection modality, as well as labelling and packaging errors.

A clinical audit was undertaken to obtain demographic data and chest X-ray results from the electronic patient database used in the Torres Strait Islands, Best Practice as well as state-wide patient information systems HBCIS, The Viewer, Enterprise PACS and XERO. Chest X-ray images without reports or notes by a TB physician directly involved in the patient's care within patient charts were reviewed by a Queensland Health TB physician to identify lung cavities.

Samples collected for AFB microscopy, culture and phenotypic drug susceptibility testing were routinely tested at the Queensland Mycobacterium Reference Laboratory in Brisbane, a WHO-designated Supranational Reference Laboratory[16]. Since November 2010, the Xpert MTB/RIF assay has been used on all new sputum smear-positive samples and, upon request, for smear-negative and extrapulmonary specimens[16].

Peripheral blood specimens were collected for HIV serology testing when possible.

Data analysis

Frequencies and percentages were calculated for age, age group, gender, country of birth, visa status and HIV serology. Descriptive statistics were generated using the Statistical Package for the Social Sciences v25 (IBM; http://www.spss.com). Diagnostic yield calculations were performed in Microsoft Excel. Incremental yield was calculated for 143 PTB cases diagnosed between 2000 and 2018. All other data were analysed using SPSS. *P*-values less than 0.05 were considered statistically significant for all tests.

Ethics approval

Ethics approval was granted in writing by the Far North Queensland Human Research Ethics Committee (HREC) (HREC/17/QCH/74-1157) and the Chair of James Cook University HREC, (H7380).

Results

Table 1 provides a summary of the characteristics of all laboratory-confirmed PTB cases diagnosed in the Torres Strait between 2000 and 2018. The majority of the patients from whom at least three sputum samples were collected were adults aged 15–59 years (106/143; 74%) and residents of PNG (114/143; 80%) with an equal gender distribution (female 73/143; 51%). Of all patients diagnosed with PTB, 60% (150/248) were PNG Treaty visitors. Nearly all Australian residents who had a diagnosis of PTB met criteria for the study, with only three excluded for not having had three sputum specimens collected. Overall, 4/248 patients diagnosed with laboratory-confirmed PTB tested positive for HIV, of whom two were included in the analysis. The remaining two HIV-positive patients were excluded as they were not diagnosed with culture-positive TB.

Table 2 shows the cumulative diagnostic yield for patients with at least three sputum specimens collected. Of these 143 patients, 42 (29%) had smear-negative PTB and 101 (71%) had at least one AFB-positive smear. Of the cases that tested AFB positive on any smear, 79% of cases yielded a positive result on the first sample and 96% of cases were positive within the first two samples. Of the 353 good quality samples that tested AFB positive on any smear, 96% of specimens yielded a positive result within the first two samples collected. Among children aged less than 15 years who tested AFB-positive on any smear, 93% of cases were positive within the first two samples. This proportion was similar regardless of quality of specimens. Overall, among the whole cohort, of the 45 poor quality specimens that tested AFB positive on any smear, 96% of specimens yielded a positive result within the first two samples collected. Of the 42 smear-negative patients, five patients had three poor quality specimens.

Table 3 provides a summary of specimen collection modality and age, and how these factors are associated with AFB smear status. The most common route of collection for the samples assessed in this study was voluntary expectoration (391; 91.14%), and 231 (59.08%) of these were AFB-positive PTB cases. The next most common collection modality was nasogastric aspiration (26; 6.06%), followed by nasopharyngeal aspirate (8; 1.86%) and induced sputum (4; 0.93%). Two of the six nasopharyngeal aspirates collected from children aged <5 years, and 2 of the 14 nasogastric aspirates collected from children aged <5 years were AFB-positive. Of children aged <5 years who voluntarily expectorated, smear-positive results were achieved from 75% of the samples collected, and of children aged 5–9 years, 33% of the samples collected were smear-positive.

Multivariate analyses of factors associated with AFB smear-positive results were performed. For all sputum specimens collected (n=429), quality samples were 3.350 times as likely to yield a smear-positive AFB result, and voluntarily expectorated samples were 5.894 times as likely to yield a smear-positive AFB result (p<0.001). Of the 429 samples collected, 76 (18%) were poor quality and, of those, 67% (n=51) were smear-negative.

Table 4 shows univariate and multivariate analyses associated with a smear-positive AFB result. Adults aged 15–59 years, PNG nationals and cavitary disease were associated with a higher odds of any smear-positive AFB result. The regression coefficient for a smear-positive result in adults aged 15–59 years was significant (p<0.05). Univariate analysis demonstrated that patients with smear-positive PTB across all age groups in this study were significantly (odds ratio 2.91; 95% confidence interval 1.12–7.60) more likely to have cavitary disease. Variables assessed in univariate analysis that had a p-value greater than 0.05 included gender, visa status, Treaty status and other age groups, and were not included in the multivariate analysis.

Clinician/clinic-based variables (registration, labelling, packaging errors) did not affect the diagnosis of PTB. Of the 429 individual samples included in the study, samples of 15 patients were affected as 44 were labelled incorrectly. Of those, 41 samples did not have collection time recorded. For the remaining three specimens with a labelling error, the specimens were not tested as the name of the patient on the pathology request form did not match the name of the patient on the specimen container. Among four samples not tested, three samples were considered too old and another leaked in transit.

Table 3.1.1 Characteristics of all patients diagnosed with pulmonary tuberculosis in the Torres Strait Islands between 2000 and 2018

Characteristic	<3 sputum specimens (n=105) (%)	≥3 sputum specimens (n=143) (%)
Age, median (IQR)	30 years (18–38)	26 years (18–38)
Age group (years)		
≤5	6 (33.33)	12 (66.67)
6–14	4 (22.22)	14 (77.78)
15–59	87 (45.08)	106 (54.92)
≥60	8 (42.11)	11 (57.89)
Gender		
Female	54 (42.52)	73 (57.48)
Country of birth		
Australia or other	2 (9.09)	20 (90.91)
PNG	103 (45.58)	123 (54.42)
Visa status		
Australian	2 (10)	18 (90)
Permanent Australian resident	1 (10)	9 (90)
PNG Treaty visitor	77 (51.33)	73 (48.67)
PNG non-Treaty visitor	23 (35.94)	41 (64.06)
Unknown	2 (50)	2 (50)
HIV serology		
Positive	2 (50)	2 (50)
Negative	69 (37.10)	117 (62.90)
Not tested	34 (58.62)	24 (41.38)

IQR, interquartile range. PNG, Papua New Guinea.

Table 3.1.2 Cumulative diagnostic yield from consecutive sputum specimens

Sputum specimen result	All patients with ≥3 sputum specimens				Children (<15 years)			
	Sputum specimens from all patients *n* (%)† *N*=143	Cumulative diagnostic yield of all specimens (%)	Good quality *n* (%) *N*=353	Cumulative diagnostic yield of good quality specimens (%)	Sputum specimens from all patients *n* (%) *N*=81	Cumulative diagnostic yield of all specimens (%)	Good quality *n* (%)† *N*=59	Cumulative diagnostic yield of good quality specimens (%)
First acid-fast bacilli smear-positive result on first sample	79 (55)	79	215 (61)	82	30 (37)	71	25 (42)	74
First acid-fast bacilli smear-positive result on second sample	18 (13)	96	36 (10)	96	9 (11)	93	7 (12)	94
First acid-fast bacilli smear-positive result on third sample	4 (3)	100	10 (3)	100	3 (4)	100	2 (3)	100
Acid-fast bacilli smear negative	42 (29)	–	96 (26)	–	39 (48)	–	25 (42)	–

† Percentages may not equal 100 due to rounding.

Table 3.1.3 Specimen collection modality, age and acid-fast bacilli smear status

Route of collection	Acid-fast bacilli negative *n* (%)	Acid-fast bacilli positive *n* (%)
Voluntary expectoration		
<5 years	1 (25)	3 (75)
5–9 years	16 (66.67)	8 (33.33)
10–14 years	11 (57.89)	8 (42.11)
15–59 years	115 (36.98)	196 (63.02)
≥60 years	17 (51.52)	16 (48.48)
Nasopharyngeal aspirate		
<5 years	4 (66.67)	2 (33.33)
5–9 years	1 (100)	0
10–14 years	0	0
15–59 years	1 (100)	0
Gastric aspirate		
<5 years	12 (85.71)	2 (14.29)
5–9 years	10 (90.91)	1 (9.09)
10–14 years	0	1 (100)
15–59 years	0	0
Induced sputum		
10–14 years	1 (100)	0
15–59 years	1 (33.33)	2 (66.67)

Table 3.1.4 Multivariate analysis of associations with a positive acid-fast bacilli smear result

Variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
Adults aged 15–59 years	3.28 (1.47–7.13)	0.004**	2.56 (1.13–5.81)	0.025*
Papua New Guinea nationals	2.84 (1.08–7.46)	0.034*	2.76 (0.99–7.66)	0.052
Cavitary pulmonary tuberculosis†	2.91 (1.12–7.60)	0.029*	2.58 (0.94–7.01)	0.066

* $p<0.05$, ** $p<0.01$
† Cavitary disease identified on chest x-rays.
CI, confidence interval. OR, odds ratio.

Discussion

This study demonstrated high sputum smear positivity among microbiologically confirmed cases, which suggests that many patients presented late for diagnosis. This was particularly true for PNG visitors who are not resident in the Torres Strait. Collection of a third sample for AFB microscopy had very poor incremental diagnostic yield and only served to unnecessarily delay treatment initiation.

As demonstrated in a univariate analysis, smear-positive PTB patients across all age groups were significantly ($p<0.05$) more likely to have cavitary disease, which contributes to a high bacillary load in sputum, and relapse and treatment failure among PTB patients[17,18]. Molecular epidemiological studies estimate that 13–20% of PTB cases are smear-negative[19]. While not as infectious as AFB smear-positive PTB, AFB smear-negative PTB can still be a source of transmission[19].

Transmission risk is an omnipresent feature of TB control activities in the Torres Strait. Although physically located in Australia, the local TB program sits on the cusp of Australia and PNG. Delivery of TB services are atypical of a standard health system in terms of access, resources and ability to recall patients across an international border. With limited opportunity to retain patients in care, it is important for microscopy and culture to perform consistently well. Although the collection of three sputum specimens increases sensitivity of smear microscopy, microscopy is also prone to false-negative AFB smear-negative results and may fail to detect TB in children and in those at risk of dying from TB[20].

Diagnostic yield is not solely reliant on the number of sputum

specimens collected. In the Torres Strait Islands, TB diagnostics and treatment delays can be attributed to inclement weather, transport inefficiencies, distance between point of collection and reference laboratories, human resource and supply chain constraints, and test reliability issues due to contaminated specimens[12]. Most of these factors could be circumvented by incorporating advanced molecular technology in the region.

Without local access to the best diagnostic equipment – Xpert Ultra – there is a risk that MDR-TB cases will be missed. In an active TB case finding study conducted in Vietnam, clinicians diagnosed 41% of TB cases using Xpert that were otherwise culture-negative[21]. Diagnostic facilities in the Torres Strait are currently absent but increasing local diagnostic capability has the potential to alleviate transmission risk and the public health burden of PTB on both sides of the international border. With its capability to diagnose TB within 2 hours, strategic placement of the Xpert Ultra in the Torres Strait should be considered to reduce a serious public health risk. Benefits include ability to rapidly diagnose the most infectious cases. Further, the Xpert assay has a sensitivity of 73% for culture-confirmed AFB smear-negative PTB cases, which would reduce the time to treat[22].

Clinician involvement in quality, collection modality, labelling errors, packaging and transport of specimens

This study confirmed that sample quality increases the potential for diagnostic yield and decreases the likelihood of missed cases. Further, an important component of AFB microscopy is that the level of infectivity of the patient is reported with smear-positive results. The smear-positive diagnostic yield for good quality specimens in this study was 96% within the first two specimens collected. Further, 96% (43/45) of poor quality specimens yielded a smear-positive result within the first two specimens collected. This suggests that poor quality should not be a contraindication for AFB microscopy; however, there is room for improvement in striving for quality specimens, which may lead to a better diagnostic yield.

In this study, 3 (0.7%) samples were not tested as they were considered too old, which is defined as samples received in the laboratory more than 7 days post-collection. The viability of sputum specimens for microscopy and culture also requires samples to be free of contamination by environmental or commensal bacteria that can inhibit the growth of *M. tuberculosis*[23]. The high humidity in the Torres Strait, in addition to more than 2000 km between collection points and reference laboratory settings, increase the likelihood that sputum specimens will be contaminated. A study conducted in Balimo in the Western Province of PNG reported TB case detection difficulties due to substandard storage and transport of specimens, which can adversely affect the viability of organisms[24]. Provision of free mandatory training in packaging and transport of specimens and adherence to pathology collection policies and procedures may help to reduce the numbers of 'no-tests' and potentially increase the diagnostic yield.

Voluntary expectoration is the preferred collection method in most passive case finding settings as the modality is cost-neutral and it is the only non-invasive approach. In this study, 91% of samples were voluntarily expectorated and were almost six times more likely to yield a smear-positive PTB result ($p<0.001$). It is unusual for young children to voluntarily expectorate; however, 28 children aged less than 10 years in this study were diagnosed with culture-confirmed PTB as a result of expectorated sputum. Of children aged less than 5 years, three (75%) were diagnosed with smear-positive PTB, and in children aged 5–9 years, one third were diagnosed with smear-positive PTB. Excessive exposure to woodfire smoke can cause a productive cough[25], and while PNG villagers frequently use woodfires for cooking, it is unknown what effect smoke inhalation had on the young children in this study.

Where voluntary expectoration is not possible, sputum induction may be an optimal choice in primary healthcare settings in the Torres Strait Islands; however, it was not frequently used during the study period and a larger study would be required to draw such conclusions. A South African study of 250 children aged 1 month to 5 years reported that specimens were easily obtained from 95% of participants and that the diagnostic yield of sputum induction followed by extraction via nasopharyngeal aspiration was superior to three gastric lavage samples[26]. When considering age-related diagnostic yield across all collection modality types, 93% of children aged less than 15 years tested AFB-positive within the first two specimens collected. A shift in clinical practice and training provision merits consideration to increase the diagnostic yield for both adults and paediatric patients.

Conclusion

Reducing the number of specimens collected will reduce unnecessary delays in treatment initiation and increase retention in care for both Torres Strait Islander and PNG PTB patients accessing health services in the TSPZ. Limiting the numbers of sputum specimens to two per patient, provided they are quality specimens, should not compromise the diagnostic yield. In patients with two negative specimens, a third should be considered in those with persistent symptoms; however, this will only be possible for Australian residents, since patient recall is not possible across the existing international border.

Improving diagnostic yield in children should be a key feature of future TB strategic plans in this remote region. Although the rate of smear positivity was impressive in children in this study, it suggests that many children with sputum smear-negative disease may have been missed. Workforce training and development using a combination of collection modalities, as well as ready access to Xpert Ultra, is critical to increase diagnostic yield in paediatric patients across the age range.

In the Torres Strait and indeed all TB programs globally, the primary goal is to identify infectious PTB patients to break the transmission cycle. With high rates of sputum smear-negative PTB diagnosed in the Torres Strait Islands, coupled with difficulties in specimen collection and extended delays in getting AFB results in the region, this study has demonstrated a need to improve diagnostic sensitivity and reduce the time to treatment initiation.

Erratum: 'the proportion of PTB that were smear-negative was high'.

Collecting only two quality sputum specimens and having ready access to Xpert Ultra testing should achieve both aims, together with rapid identification of drug-resistant TB, which is a challenge in this setting[7].

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Figure 4.1 Boigu Island, Torres Strait Islands, Australia (Foster, 2016).

Chapter 4: The Rise of Drug Resistance

Overarching Aim #1: Investigate cross-border TB disease epidemiology.

Overarching Aim #2: Identify opportunities for evidence-based enhanced policy and practice for the management of TB in the region (Translational Research).

Overarching Aim #3: Identify opportunities for strengthened cross-border communication and collaboration between Australia and PNG health services to better manage TB in the region.

Aims:

1. Provide a geospatial map that demonstrates the rise of drug-resistant TB in the region over the past two decades.
2. Explore drug-resistant TB diagnosed in the Torres Strait between 2000 and 2020
3. Explore factors that contribute to mono and multi-resistant TB.
4. Determine time to treat using comparison of median delays and selected variables that contribute to total time to treat via Time to Event analyses.
5. Identify variables that contributed to excessive delays in the diagnostic and treatment pathway.
6. Explore factors that contribute to poor outcome in patients with drug-resistant TB.

4.1 Spatiotemporal trends of drug-resistant TB in the Torres Strait Islands, Australia and Papua New Guinea border region between 2000 and 2020

4.1.1 Aims

1. Provide a geospatial map that demonstrates the rise of drug-resistant TB in the region over the past two decades.
2. Explore drug-resistant TB diagnosed in the Torres Strait between 2000 and 2020.
3. Explore factors that contribute to mono and multi-resistant TB.

In the first section of this chapter, I provide spatiotemporal mapping of the residence of all cases of drug-resistant TB (DR-TB) diagnosed in health facilities in the Torres Strait Protected Zone from 2000 to 2020. I use information collected from the Notifiable Conditions System to demonstrate the rise in drug-resistance over time. I identify predictors of different types of DR-TB and determine patients most at-risk of DR-TB in the region. Outputs of the analyses are that 1) DR-TB cases have spread geographically over time; 2) the closest PNG village to Australia is not where the majority of DR-TB cases are diagnosed; 3) isoniazid resistant TB rose to its highest prevalence point in 2011, when it surpassed multidrug-resistant TB (MDR-TB) as the dominant strain in the study group; 4) no further isoniazid-resistance was identified after 2015; 5) compared with non-Rif R, being male and having previously been treated for TB are associated with rifampicin resistance; 6) even in new cases, 65% are rifampicin resistant which is indicative of DR-TB transmission at the community level and 7) rifampicin-resistance is often accompanied by resistance to ethionamide.

4.1.2 Contribution

- I wrote the ethics and site-specific authorisation applications to use data for this study.
- I contributed to the design of this study.
- I collected all data used in this study.
- I was the lead author of this study which I initially drafted.
- I shared this chapter with my supervisory team to review.
- I obtained clearance to share applicable data with software developer M.M.
- I worked collaboratively with software developer M.M and provided names of islands and villages to determine longitude and latitude of place names for plotting in Carti software.
- I plotted data points in Carti software to generate geospatial maps of case data in the region.

Results from this study are below.

Spatiotemporal trends of drug-resistant TB in the Torres Strait Islands, Australia and Papua New Guinea border region between 2000 and 2020

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Abstract

Introduction

Papua New Guinea (PNG) is experiencing a widespread drug-resistant tuberculosis (DR-TB) epidemic. In the Western Province, close to the border with northern Australia in the Torres Strait, Daru Island has one of the highest incidence rates of DR-TB and multidrug-resistant TB (MDR-TB) worldwide. PNG nationals living in this region often present to Australian Primary healthcare facilities in the Torres Strait to access TB diagnosis and care. We sought to map the spatiotemporal distribution of DR-TB cases diagnosed in the Torres Strait and to describe patterns observed among DR-TB cases.

Methods

All residents of the Torres Strait Islands and PNG nationals who presented to health facilities in the Torres Strait and were diagnosed with DR-TB between 2000 and 2020 were included in the study. Types of DR-TB diagnosed over four different time periods were plotted on maps using Geographical Positioning System tools to demonstrate the rise and distribution of multidrug-resistant TB. Possible predictors of DR-TB were analysed using binary logistic regression.

Results

Of 133 patients diagnosed with DR-TB in the Torres Strait between 2000 and 2020, 124 (93%) were PNG nationals and 9 (7%) were Australian nationals. The fact that 107 (80%) DR-TB cases had no history of previous treatment, suggests primary transmission of drug-resistant strains. Across the study period, RR/MDR-TB was the most common form of drug resistance detected, representing 93 (70%) cases. The village origin contributing the largest number of RR/MDR-TB cases 40/93 (43%) was Mabadauan village. Intriguingly the neighbouring Sigabadaru village, which is a Treaty village of similar size and ease of access to TB services in the Torres Strait, had low case numbers. Twice as many women were diagnosed with RR/MDR-TB (OR 2.2; *p* .04), although the gender balance was reversed among cases with isoniazid mono-resistance.

Conclusion

DR-TB transmission observed on both sides of the border is a concern, although DR-TB case numbers are far lower on the Australian side and have reduced with improved services established on Daru Island. Context-specific anomalies such as gender specific differences and high variability in the number of DR-TB cases detected from different PNG villages indicate a need for qualitative research to better understand the situation on the ground and guide more effective control efforts.

Introduction

Tuberculosis (TB) is an infectious disease of global public health significance.[1] It is the second leading cause of death from an infectious agent, surpassed only by COVID-19.[2] An estimated 10.6 million TB cases were diagnosed in 2021 and, of those, 450,000 cases were rifampicin-resistant (RR) / multidrug-resistant (MDR) – TB disease that is resistant to both isoniazid and rifampicin.[1] The burden of drug-resistant (DR)-TB has important implications for the Global End TB Strategy, which aims to reduce the incidence of TB by 90% by 2035.[3] Although standard short-course treatment regimens for drug-susceptible (DS)-TB can cure up to 90% of cases,[4] a higher frequency of unfavourable outcomes including treatment failure and death have been reported for MDR-TB cases.[5]

During the period of our study, treatment of DR-TB and RR/MDR-TB required costly second line antibiotics of which only a small arsenal were available, including fluroquinolones,

ethionamide (ETO) and aminoglycosides.[4,6] Cessation of treatment can lead to spontaneous reactivation and resistance to anti-TB drugs, thus treatment completion is the most effective plan to treat TB.[7] However, at the time this study was conducted, treatment of RR/MDR-TB would take up to 20 months to complete and treatment success could be complicated by non-adherence and undermined by associated side effects and high costs.[4,6]

In 2014, the World Health Organization (WHO) declared a TB emergency in Papua New Guinea (PNG) which has the highest TB incidence rate in the Pacific region.[8,9] In the same year, Daru Island in the Western Province of PNG was identified as a TB 'hot-spot'.[9,10] A body of water known as the Torres Strait separates the Western Province of PNG from the Torres Strait Islands of Australia. Daru General Hospital is strategically important to TB control in the Torres Strait as it is the main referral hospital for PNG residents of villages adjacent to the Australia border. Residents from Treaty villages can freely travel in both directions across the open international border, while residents from non-Treaty villages do not have permissions to enter the Torres Strait Islands for traditional purposes, but some cross the border to seek healthcare.[11] Although the incidence rate of TB on mainland Australia is 5.5 cases per 100,000 population,[12] the rate in the Indigenous population of the Torres Strait Islands in 2014 was 107 cases per 100,000 population[13] and the high DR-TB case load in the Western Province is a significant biosecurity issue for Australia.

Up until 2008, MDR-TB was not considered a public health issue by the PNG Government; while TB could be diagnosed by basic sputum smear, drug resistance was neither detected nor reported in Daru Hospital in PNG as culture and drug susceptibility testing (DST) were not routinely available.[14] Treatment of all TB cases with first line drugs was attempted, however successful treatment of drug susceptible (DS)-TB cases was threatened by capacity issues and inadequate drug supply.[15] In 2008, Australian delegates travelled to Daru Island to report that PNG nationals from the Western Province had been diagnosed with MDR-TB in the Torres Strait. From 2009, isolates from Daru Hospital were sent to the Queensland Mycobacterium Reference Laboratory (QMRL) in Brisbane for culture and DST.

Although DR-TB diagnostics for PNG nationals presenting to Daru Hospital were available from 2009, treatment for MDR-TB was not available to residents of Daru Island and surrounding PNG villages until 2012.[15] The advantage of close-proximity to the Torres Strait for residents of the Treaty villages was easier access to MDR-TB treatment via the Queensland Health led TB outreach clinics on the Australian side of the border. In 2012, the Australian

Government Aid program committed AUD $14.3 million to upgrade Daru General Hospital and construct a 22-bed TB ward to improve PNG's TB diagnostic and treatment capacity.[16] Thereafter, PNG patients who presented to health facilities in the Torres Strait were diagnosed in the Torres Strait and referred back to the PNG health system for ongoing care (Figure 4.1.1).

Transmission of DR-TB across the PNG-Australia border is still in its early phase.[17] However recent whole genome sequencing of DR-TB strains from the region has confirmed ongoing transmission and detection of DR-TB at the cross-border has increased over the past two decades.[17,18] While global DR-TB epidemiological studies have focused largely on the role of RR/MDR-TB in the TB epidemic,[19] it is possible that resistance to other TB drugs is associated with ongoing transmission and enhanced virulence.[17] Responses to emergent DR-TB strains rely upon regional case notification data and assessment of the trends that are driving the epidemic.[4,6] Therefore, more evidence is required to understand the local epidemiological profile of DR-TB, identify at-risk individuals, improve programmatic TB responses and patients' outcomes.[17]

The aim of this study was to determine the distribution of DR-TB diagnosed in the Torres Strait over two decades and describe patterns among DR-TB cases. We anticipate that evidence derived from this study will help local TB programs with planning, monitoring and improving the management of patients presenting to health facilities in the Torres Strait Island who are most at-risk.

Methods

This retrospective study evaluated health data from all residents of the Torres Strait and PNG villages adjacent to the Australia / PNG border who were diagnosed at an Australian primary health centre (PHC) in the Torres Strait with laboratory-confirmed DR-TB between March 2000 and March 2020. There have been four different models of TB care used in the region over the past two decades.[20] Residents of PNG villages external to the Western Province of PNG who did not enter the Australian health system via a PHC located in the Torres Strait Protected Zone (TSPZ) were excluded.

Data collection

Notifiable disease data were extracted from the Queensland Notifiable Conditions System (NOCS) under a Public Health Act authorisation (QCH/36155 – 1157), and drug-resistance

patterns were cross-checked in Queensland Health's laboratory system, AUSLAB, considered the source of truth by the research team. Acid-fast bacilli (AFB) testing results were also obtained from AUSLAB. Patient notes available in the electronic patient records system used in the Torres and Cape Hospital and Health Service, Best Practice, were accessed to retrieve 'village of residence' of patients diagnosed with DR-TB. As Best Practice is linked with Queensland Health's patient registration system, HBCIS (Hospital-Based Corporate Information System), Best Practice was considered the source of truth for village of residence by the research team.

Coordinates of patients' villages of residence were obtained using Geographical Positioning System (GPS) tools. These coordinates were cross checked with maps used by the Australian Department of Foreign Affairs (DFAT) which has joint responsibility with the Government of PNG to govern the Torres Strait Treaty.[21,22] The small population of some of the villages and a lack of identifiable infrastructure via satellite placed limitations on using GPS tools in very remote locations. Any deviations between GPS placement of villages and DFAT placement of villages were further cross-checked by the Cross Border Communications Officer (author DP) employed to manage cross-border related health issues in this region.

Specimens collected in Queensland Health facilities during the study period were sent to the QMRL in Brisbane for mycobacterial culture and phenotypic drug susceptibility testing from 2000. Genotypic testing - Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) was available in QMRL from November 2010. Routine Ziehl-Neelson smear microscopy was performed at either Cairns Hospital, Townsville Hospital or QMRL during the study period. Further information about specific QMRL laboratory processes for TB isolates are reported elsewhere.[23]

The last population Census undertaken in PNG was in 2011, and these figures are now outdated. Ascertaining population data in the Treaty villages has reportedly been challenging due to residents referring to different criteria at different times. The number of people that claim a village as their home might be different to the number of people that reside in the village with many living in designated 'corner' villages on Daru Island.[24] In 2020, an Australian company Inloc pty.ltd. based in Cairns and that operates a Ranger Program in the Treaty villages, undertook a food distribution activity while the international border was closed to Australia due to the COVID-19 pandemic.[24] For the purpose of this study, and with permission, we have used Inloc's population numbers for the Treaty villages (box 1).

Box 1. Definitions

New case (primary transmission): the individual has not previously been treated for TB or taken anti-TB medication for less than one month so transmission has occurred directly from a person with active drug-resistant TB disease.[25]

Previously treated case (acquired): drug-resistance has been acquired due to poor treatment compliance or previous treatment interruptions during TB treatment.[25]

Drug-resistant TB hot-spot: concentrated areas of DR-TB per-capita incidence.[26]

Resistance types[25]:

Hr-TB: *M.tuberculosis* (MTB) strains resistant to isoniazid and susceptible to rifampicin

MDR-TB: MTB strains resistant to at least isoniazid and rifampicin

RR: MTB strains resistant to at least rifampicin. RR-TB cases may be resistant or susceptible to isoniazid

ETO-R: MTB strains resistant to at least ethionamide

Strep-R: MTB strains resistant to only streptomycin in this study

DR-TB: MTB strains that are resistant to any anti-TB drug

DS-TB: MTB strains that are susceptible to rifampicin and isoniazid

Analyses

Statistical analyses were performed using IBM SPSS Statistics, version 27 (2019, Armonk, New York, United States). Frequencies and percentages were calculated for categorical data including isoniazid mono-resistant TB (Hr-TB), rifampicin mono-resistant TB (RR-TB), MDR-TB and streptomycin mono-resistant TB (Strep-R). Spatiotemporal trend analyses were performed to demonstrate trends of drug-resistance over time in the region.

As DR-TB was found to be associated with unfavourable treatment outcomes in this cohort in a previous study,[27] we sought to determine if case type and gender were predictors of specific types of DR-TB. We assessed for resistance to: isoniazid, rifampicin and ethionamide. We also had a separate category for both isoniazid and rifampicin resistance (MDR-TB). Pearson's chi-square tests were used on all gender-based analyses and to determine an association between case type and MDR with ethionamide-resistant (ETO-R) TB. Two-sided Fisher's exact tests were used on all remaining case type analyses to determine possible associations between case type and different types of DR-TB diagnoses.

Univariate and multivariate analyses of gender and case type as possible predictors of DR-TB were stratified by each type of drug-resistance and performed using binary logistic regression. The level of significance was set at $p < 0.05$ for all analyses.

Ethics

Ethical approval was obtained from the Far North Queensland Human Research Ethics Committee (HREC) (HREC/17/QCH/74-1157), and by James Cook University HREC, Townsville, Australia (H7380).

Results

Of 133 patients diagnosed with DR-TB during the study period, nine (7%) were residents of Australia and 124 (93%) were residents of PNG, with 86/124 (69%) of PNG nationals residing in a Treaty village. Overall, 107 (80%) DR-TB cases were new, indicating primary infection of drug-resistant strains, the remaining 26 had received full or partial treatment previously, indicating potentially acquired resistance. Demographics and characteristics of the 133 DR-TB patients diagnosed between 2000 and 2020 in the Torres Strait Islands are reported elsewhere.[13,27]

Between 2000 and 2020, MDR-TB was the most common form of DR-TB diagnosed in the Torres Strait / PNG border area (Figure 4.1.2). Isoniazid-only resistance peaked in 2011 at which time approximated equal numbers of MDR-TB and Hr-TB were diagnosed. No further cases of Hr-TB were diagnosed after 2014. Major peaks in MDR-TB diagnoses occurred in 2007, 2010 and 2018. All villages except the non-Treaty village of Irupi recorded at least one case of MDR-TB that was also ETO-R.

Table 4.1.1 shows the number of patients coming from the PNG villages. One of the villages closest to the Australian border, Mabadauan, was home to 53 patients in the cohort. Interestingly, neighbouring Sigabadaru which is the closest PNG village to the Australian border (Figure 4.1.3), had only four DR-TB cases diagnosed in the Torres Strait over two decades. Other DR-TB hot-spots with >10 cases identified were in residents of Daru Island and Ture Ture. The visual depiction of the geographical distribution of DR-TB over two decades in the Torres Strait / PNG border region is shown in Figures 4.1.S1 to 4.1.S4.

The first case of DR-TB in an Australian resident of the TSPZ was diagnosed in 2006 with Hr-TB. An Australian resident diagnosed with Strep-R TB in 2012 was later diagnosed with MDR-TB in 2013. Table 4.1.1 shows that overall, 78% of DR-TB cases diagnosed in Australian residents occurred between 2013 and 2018. A high rate of comorbidities was found in the nine Australian DR-TB diagnoses between 2006 and 2018: two had leprosy, one was classified as obese, one had hepatitis B and one had renal disease and diabetes mellitus type II.

Females were twice as likely to have RR/MDR-TB (OR 2.2; *p* .04) than males and Hr-TB without additional resistance was significantly associated with males (*p* .007). Patients who had not previously been treated for TB were nearly four time as likely to have RR (aOR 3.989; *p* .03) and three times as likely to have ETO-R (aOR 3.3.6.1; *p* .02), indicating primary transmission as the driver of the epidemic. Sixty-five percent of new cases were resistant to rifampicin. All cases of ETO-R were identified in MDR-TB cases, and only nine MDR-TB cases were not resistant to ETO.

Discussion

In investigating the distribution of DR-TB cases diagnosed in the Torres Strait / PNG border over two decades (2000-2020), we found variations across all resistance patterns over time. We also found an unexpected and uneven distribution geographically with hot-spots of DR-TB cases. We identified a greater density of DR-TB cases in certain villages at specific times, prompting a review into characteristics of disease notifications and the population in these highly concentrated areas. Identifying hot-spots may be useful for targeted TB prevention and control strategies.

In our study DR-TB hot-spots identified in three specific areas on the PNG side of the international border – Daru, Mabadauan and Ture Ture. Other spatiotemporal studies have shown that TB hot-spots tend to include neighbouring communities, particularly those with similar socio-demographic characteristics[28]; however, this occurrence was not observed in this study. Both Mabadauan and Sigabadaru are Treaty villages of similar size with ease of access to the same PHC in the TSPZ. The reasons for uneven distribution of DR-TB and few case notifications over two decades in villages in such close-proximity to each other in our study are unclear, but may be related to sociocultural, ethnographic and geopolitical factors. It is possible that connectedness rather than distance predicts the spread of disease where human movement and the social, trade and environmental constructs that support it, can both reveal

and conceal risk. For example, congregate settings such as health facilities on Daru (a hospital) and Mabadauan (a small health centre) may have acted as conduits for DR-TB transmission into these communities.

Difficulties accessing medical resources often account for uneven distribution of TB among communities[29] but in our study, two of the three DR-TB hot-spots are home to major health facilities in the region relative to their populations. Although the region's major hospital is located on Daru Island, so too are corner villages assigned to some of the Treaty villages.[30] As our study assigned location of residential address to each case, it is possible that some of the Daru cases diagnosed were from the Treaty villages. Nevertheless, our results are in keeping with experiences of Daru Island residents seeking referrals for treatment to the Australian TB program run from Saibai and Boigu Islands in the Torres Strait.[30] When the TB clinics on Saibai and Boigu closed in 2012, nearly half of the 92 patients referred to the PNG health system for continuation of care, were from Daru and more than three quarters of these had MDR-TB.[30] Saibai Island is the only location in the Torres Strait Islands, Australia, to have had DR-TB diagnoses.

Spatiotemporal dissemination of TB has been linked to transportation infrastructure and heavily populated transportation routes in other settings.[28,31] While there are no roads connecting communities in this region, distinct routes of transportation are by sea and typically by small, motorised boats.[32] Designated fuel points are located in Mabadauan, Daru and Ture Ture which may help to explain higher numbers of DR-TB cases in these three locations. Ture Ture has high traffic of visitors, particularly when Mabadauan runs out of fuel, and it becomes a primary stopping point for motorised shipping. It also has fishing and trade partnerships with residents from TB-endemic Merauke in Papua Province, Indonesia. Further research is needed to examine the factors leading to geographical TB hotspots.

Spatiotemporal surveys generally focus on the spread of AFB-positive cases as smear positive TB disease indicates a higher bacillary load and increased infectiousness when compared with smear negative TB disease.[33] While we included smear negative and extrapulmonary cases in our study, nearly two-thirds of DR-TB patients were AFB positive. Although we observed a high rate of primary DR-TB transmission on both sides of the border, DR-TB case numbers were far lower on the Australian side. Of all DR-TB cases mapped, nearly half were diagnosed in PNG residents living within 20 minutes by small motorised boat from the Torres Strait Islands in Australia.

Despite close interactions between residents of each country, there was a substantial delay between the first MDR-TB case diagnosed in a PNG national (2001) and the first MDR-TB case diagnosed in an Australian resident (2013). It should be noted that one published article suggests that an earlier PNG case was diagnosed in the region in 1984[23]; however, no laboratory evidence is available to support this finding. Factors that contributed to the protection of Torres Strait Islanders from DR-TB transmission are unknown given the frequency of contact between residents of both countries in this region.

During the study period, weekly trade markets were held on the shorefront of Saibai Island and slightly further inland on Boigu Island, which were well-attended by women of the PNG Treaty villages. It is possible that the open-air nature of the market interaction here provided some level of protection against transmission. Qualitative investigation is recommended to further understand connectedness and identify sociocultural drivers of DR-TB transmission in this region that may provide clarity on micro-environments of each village differing from one another in terms of social history, clan warfare, tribal associations, Christianisation and access to health care.

Females in the region were twice as likely to have MDR-TB than males, which is incongruent with global trends.[34] Females of reproductive age (15-49 years)[35] were disproportionately affected by DR-TB in this study. Although we did not collect data on pregnancy status, the high proportion of DR-TB in women of child-bearing age poses risks associated with greater numbers of orphans and impacts on societal and economic structures.[36] It is possible that gender disparities in case notifications were due to social and cultural constructs of women remaining at home to tend to the sick in PNG Treaty villages, thus increasing the likelihood of exposure.[34] Qualitative research to illuminate factors associated with traditional roles of women this should be explored. Future studies could investigate whether this is an ascertainment bias (in which women are more likely to present with MDR-TB) or greater risk in women owing to sociological factors such as occupational and familial contact structures.

In this study, new cases were three times as likely to have ETO-R, indicating that ETO-R may be a more recent phenomenon of primary transmission. Of those tested, nearly all MDR-TB cases were resistant to ETO (80/86) and the lack of Hr-TB cases diagnosed after 2014 may be a result of ineffective TB control and inadequate use of TB treatment regimens that led to the replacement of drug-susceptible TB with DR-TB.[29] In an effort to stop the cycle of transmission-infection-reinfection and improve treatment outcomes, the WHO in 2016

recommended that all patients diagnosed with RR be treated with an MDR-TB regimen regardless of isoniazid resistance.[37] This may help to explain the reduction and then cessation of Hr-TB cases after 2014 in this study however, RR-TB became so widespread so quickly and predominated all other types of resistance over time.[38]

Limitations

An important limitation of this study is that it was not a population-based incidence study, but relied solely on case presentations to Australian health facilities. As such it represents a highly select sample and may not be representative of the situation on the ground in PNG. The Torres Strait Treaty does not routinely permit visitors from non-Treaty villages into Australian waters, which likely explains the reduced number of DR-TB cases from non-Treaty compared to Treaty villages.

This study did not include DR-TB cases diagnosed by the PNG health system, nor did it include DS-TB cases diagnosed in either country; therefore, we cannot make assumptions about the burden of disease. External factors may explain why some residents were more inclined than others to access health services in the Torres Strait Islands and, although this may help to explain higher case load in some villages, we were unable to explore this possibility. We focused this study on spatiotemporal analysis, with brief consideration of gender and case type as other factors have been considered elsewhere[13,27] whereas these variables were not previously considered.

Conclusion

To date, cross-border DR-TB transmission into Australia has been limited and restricted to Saibai Island only. Nevertheless, it is important to monitor from a programmatic perspective. Transmission risk is likely to be dependent on village connectedness and drivers of people movement rather than geographical proximity to high incidence villages. Context-specific spatiotemporal patterns identified in this study include gender specific differences and high variability in the number of DR-TB cases among PNG nationals from different Treaty villages. Qualitative research may provide a better understanding of these anomalies and assist planning for better resource allocation and patient-centred DR-TB care.

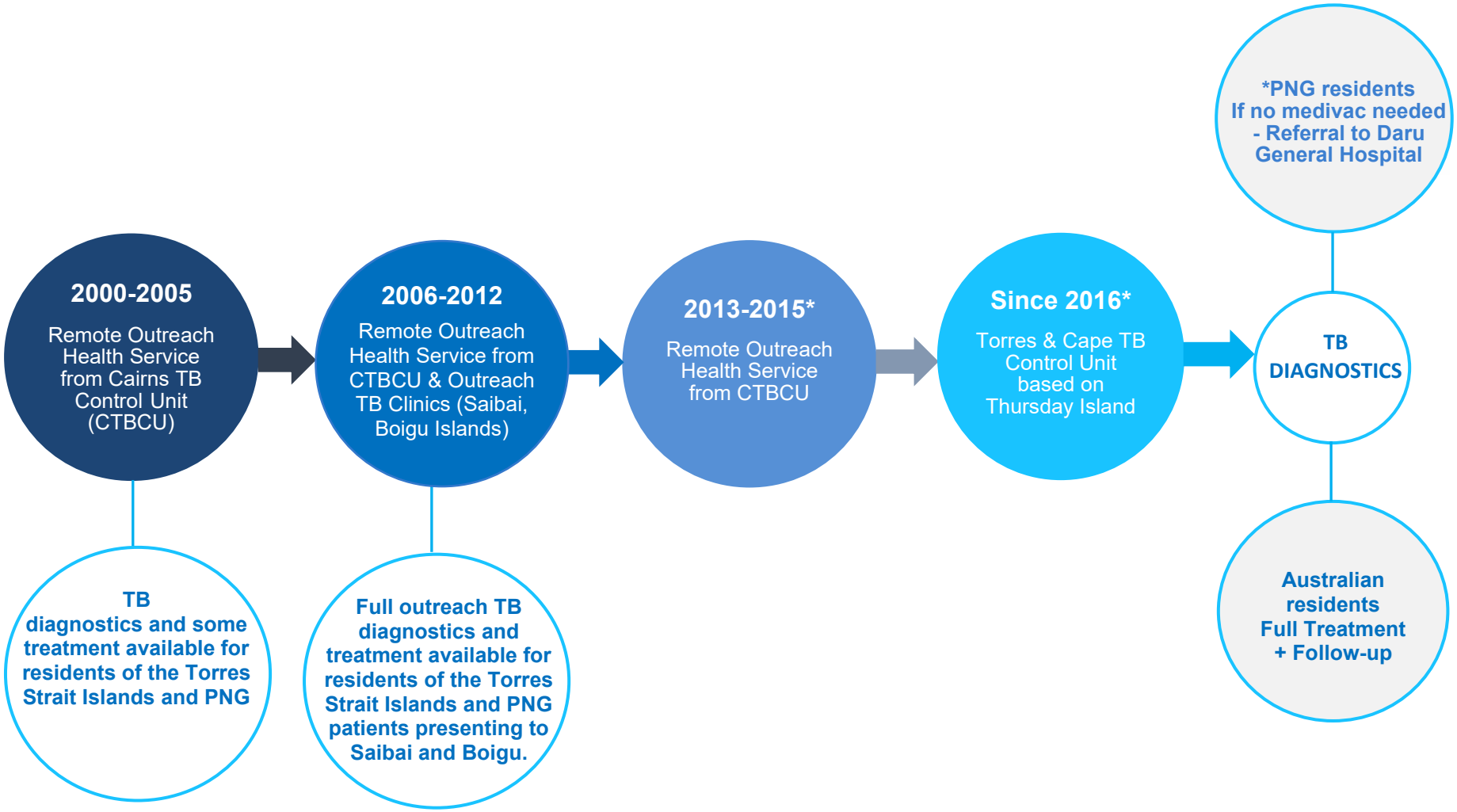

Figure 4.1.1 Description of the different tuberculosis programmatic time periods in the Torres Strait / Papua New Guinea cross-border region between 2000 and 2020

Note. TB, tuberculosis; PNG, Papua New Guinea.[1] DOI. 10.6084/m9.figshare.16834648

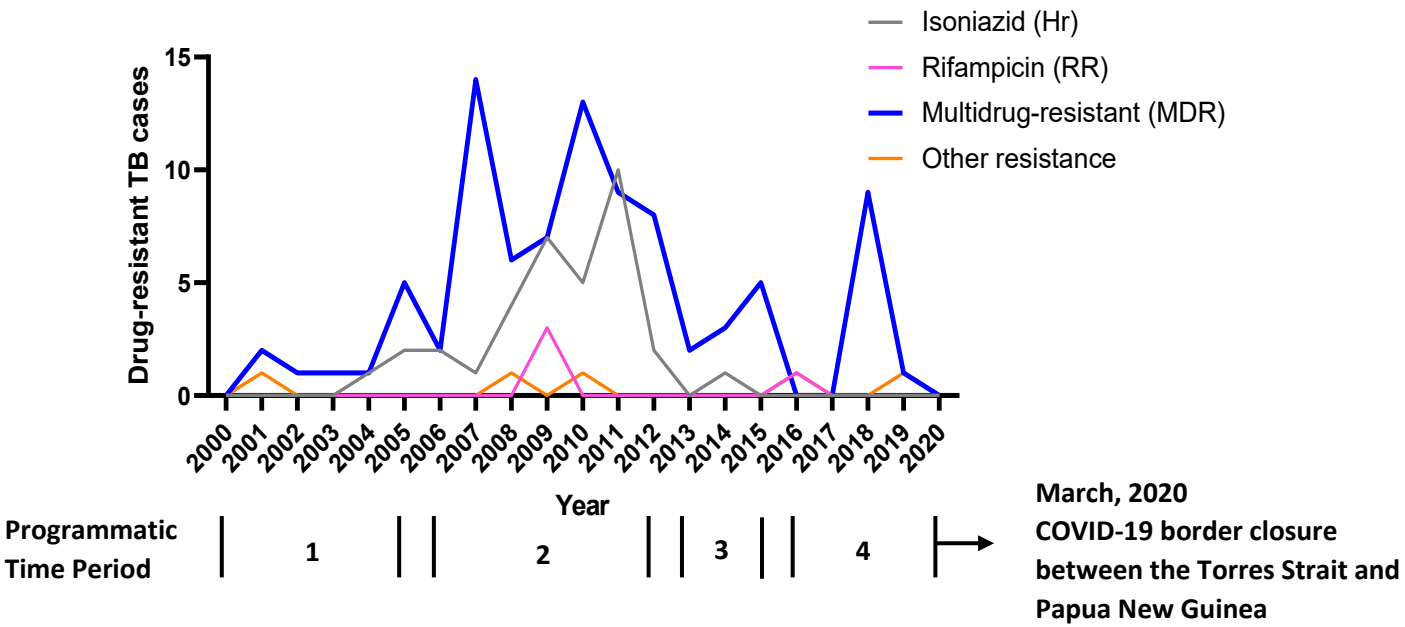

Figure 4.1.2 Variable number of drug-resistant TB cases diagnosed in Australian health facilities in the Torres Strait Protected Zone from 2000-2020, during different programmatic time periods

Note. Other resistance – streptomycin mono-resistant tuberculosis

Table 4.1.1 Drug-resistant TB case numbers from different Papua New Guinea Treaty and non-Treaty villages and Australian Torres Strait Island inhabitants diagnosed in the Torres Strait between 2000 and 2020

	2000-2005 (N=14)				2006-2012 (N=96)				2013-2015 (N=11)				2016-2020 (N=12)				Total
	Hr-TB	RR	MDR	Other	Hr-TB	RR	MDR	Other	Hr-TB	RR	MDR	Other	Hr-TB	RR	MDR	Other	
Buzi[#]	0	0	1	0									0	0	1	1	**3**
Dimiri[&]	0	0	4	0	1	0	6	0									**11**
Sigabadaru[#]	0	0	1	0	1	1	1	0									**4**
Mabadauan[#]	2	0	3	1	9	0	29	0	1	0	6	0	0	1	1	0	**53**
Daru Island[&]	0	0	1	0	7	0	7	0					0	0	1	0	**16**
Parama[&]	1	0	0	0	1	0	0	0					0	0	1	0	**3**
Saibai Island*					1	0	0	1	0	0	4	0	0	0	3	0	**9**
Kurunti[&]					0	0	1	0									**1**
Kulalai[&]					0	0	2	0									**2**
Irupi[&]					0	0	0	1									**1**
Old Mawatta[#]					2	0	1	0									**3**
Ture Ture[#]					8	0	7	1									**15**
Kadawa[&]					1	0	1	0									**2**
Katatai[#]					0	0	2	0									**2**
Ngao[&]					0	2	0	0					0	0	1	0	**3**
Kiwia[&]					0	0	2	0									**2**
Kibuli[&]													0	0	1	0	**1**
Woidoro[&]													0	0	1	0	**1**
Total	3	0	10	1	31	3	59	3	1	0	10	0	0	1	10	1	**133**

Note. *Australian Torres Strait Island; [#]Treaty village; [&]non-Treaty village; Hr-TB – isoniazid mono-resistant TB; RR – rifampicin mono-resistant TB; MDR – multidrug-resistant TB; Other – streptomycin mono-resistant TB; 2006-2012, Saibai and Boigu TB clinics were open to Papua New Guinea nationals for TB care management

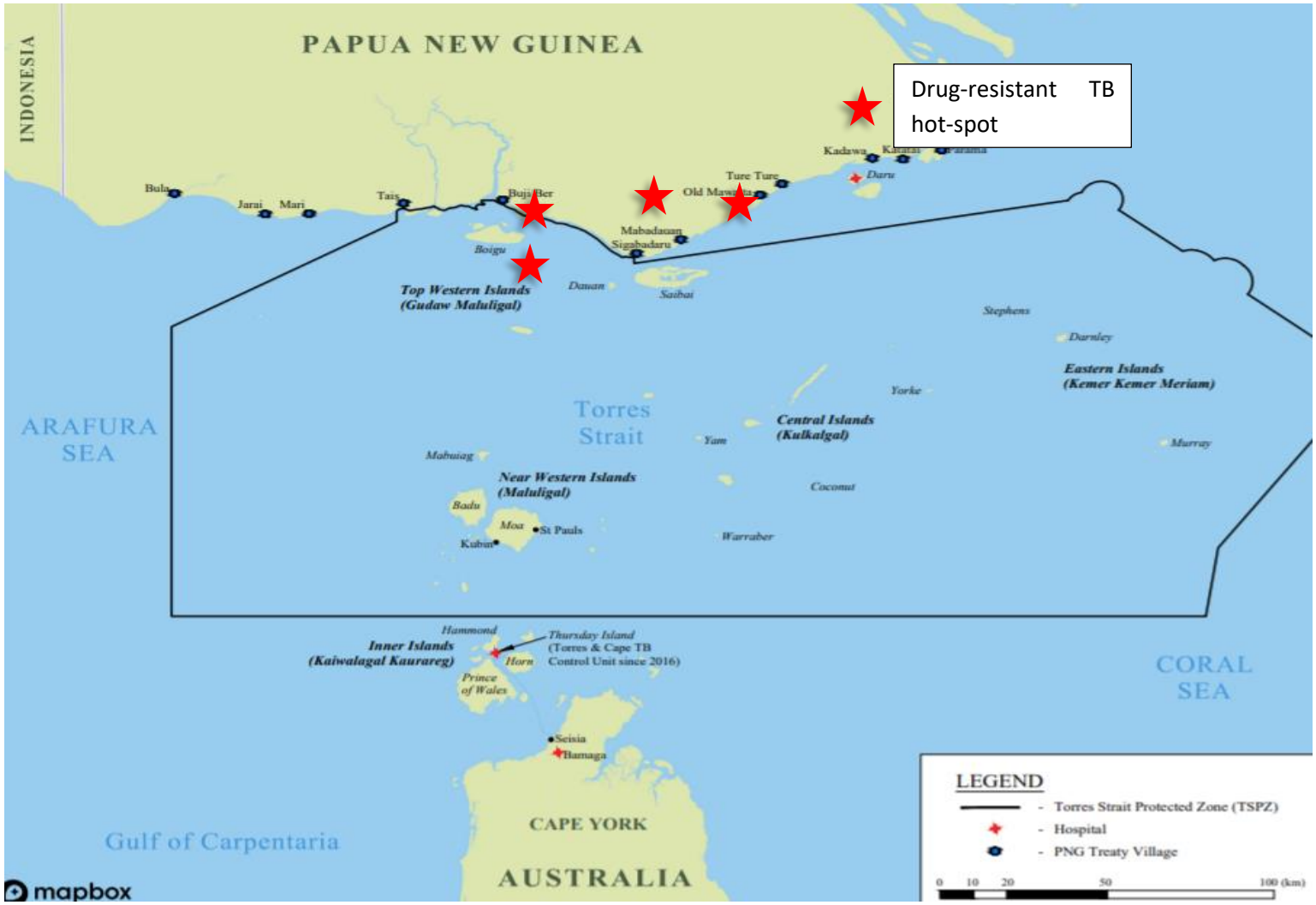

Figure 4.1.3 Distribution of drug-resistant TB hot-spots across the Torres Strait / Papua New Guinea border region

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Box 4.1.S1. Population estimates: Australia / PNG border communities with DR-TB diagnoses between 2000 and 2020

Papua New Guinea Treaty Villages – population[24]

Western Treaty villages: Bula, Jarais, Mari, Tais, Buji / Ber; population 1979

Central Treaty villages: Mabadauan, Sigabadaru; population 2621

Eastern Treaty villages: Old Mawatta, Ture Ture; population 1040

Far Eastern Treaty villages: Kadawa, Katatai, Parama, Sui; population 3316

Papua New Guinea non-Treaty Villages

Non-Treaty villages included in this study: Dimiri, Irupi, Kibuli, Kirunti, Ngao, Woidoro

Islands: Daru Island - population 15,142[27] is located in the Western Province of PNG and is not a Treaty village; population

Australia

Islands: Saibai Island - population 340[28] is located in the Torres Strait Islands, Australia and is the only Australian community included in this study.

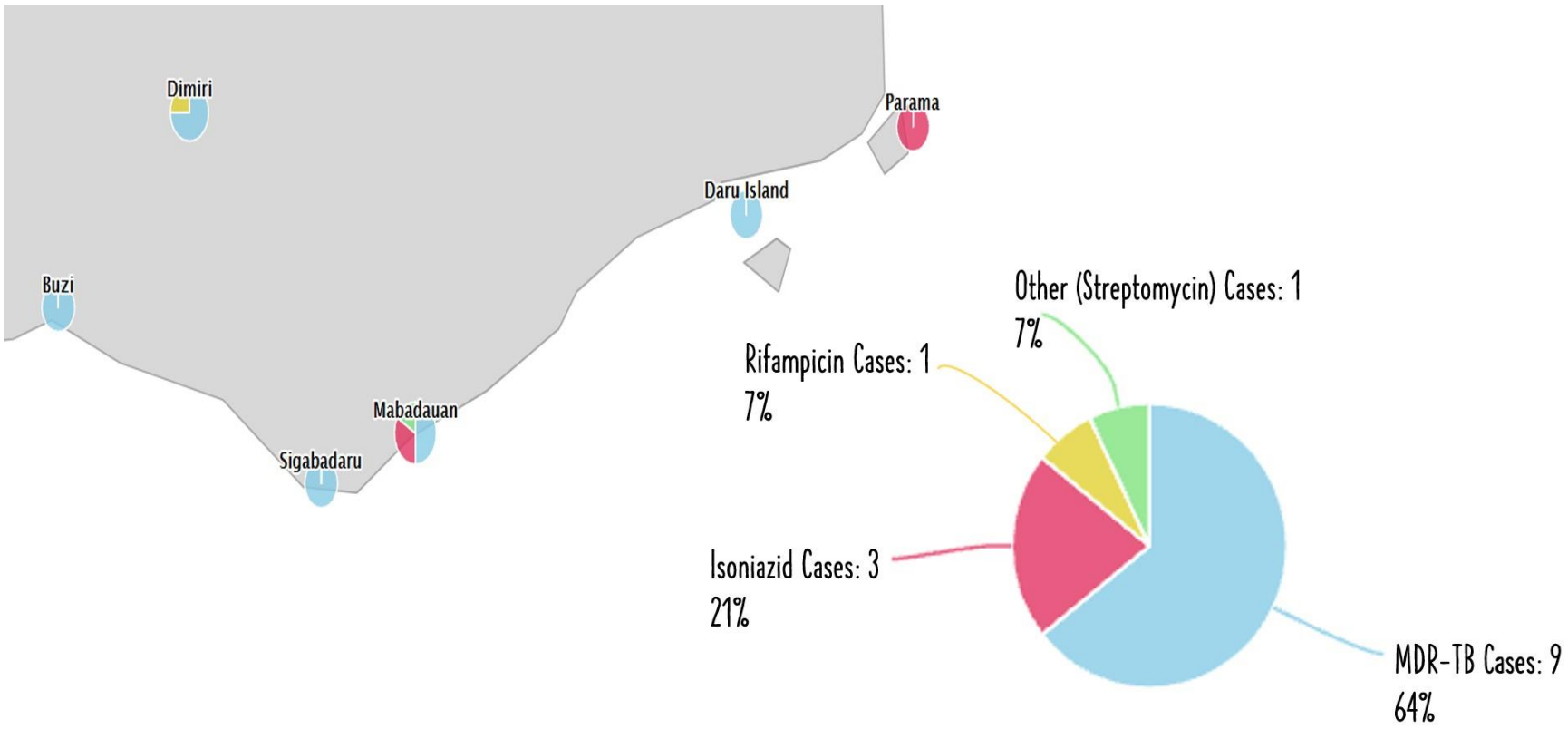

Figure 4.1.S1 Distribution of drug-resistant tuberculosis and residential location of cases diagnosed in Australian health facilities in the Torres Strait Protected Zone from 2000-2005

Figure 4.1.S2 Distribution of drug-resistant tuberculosis and residential location of cases diagnosed in Australian health facilities in the Torres Strait Protected Zone from 2006-2012

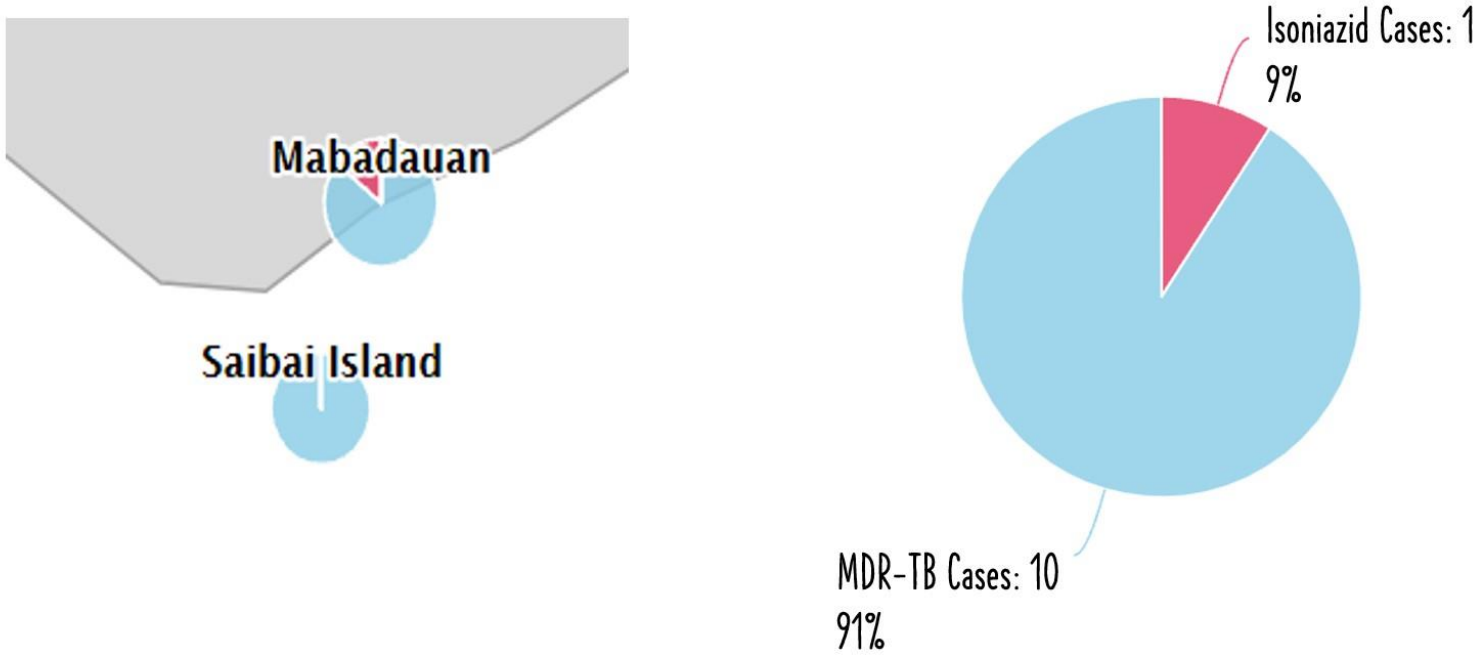

Figure 4.1.S3 Distribution of drug-resistant tuberculosis and residential location of cases diagnosed in Australian health facilities in the Torres Strait Protected Zone from 2013-2015

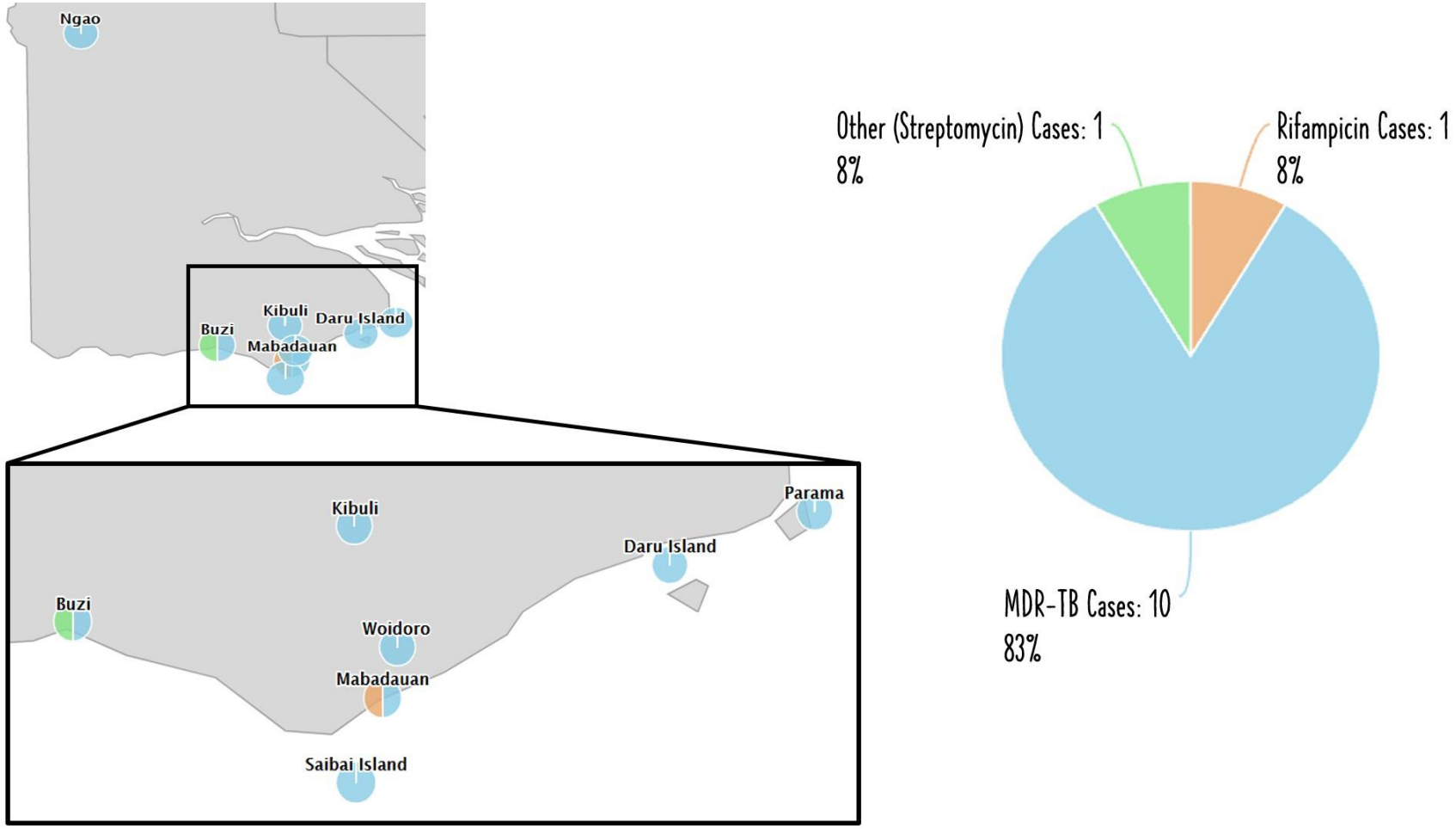

Figure 4.1.S4 Distribution of drug-resistant tuberculosis and residential location of cases diagnosed in Australian health facilities in the Torres Strait Protected Zone from 2016-2020

Further discussion not included in the published manuscript

The combination of isoniazid and ETO-R in MDR-TB patients is consistent with other studies.[1,2] Typically, the acquisition of drug-resistance in a previously treated TB case is the result of inadequate or incomplete DS-TB treatment; however, both isoniazid and ethionamide are pro-drugs that share common pathways but need to be activated by different enzymes.[2] This physiological process can lead to cross-resistance and patients can be resistant to InhA without ever having been exposed to ethionamide.[3] ETO-R is a product of historical use of ethionamide in first-line regimens, and InhA is a gene mutation associated with isoniazid-resistance that is often found in highly transmissible MDR-TB strains.[4]

Understanding drug-resistance patterns and associated gene mutations, particularly those involving isoniazid, is important for physicians treating MDR-TB because prescribed treatment regimen may need to be different if gene mutation has occurred.[5] High level Hr-TB occurs when Hr-TB confers katG mutations, whereas low level Hr-TB occurs when Hr-TB confers InhA mutations.[6] A study conducted in South Africa suggests that patients infected with the katG mutation are unlikely to benefit from high-dose isoniazid treatment but may benefit from ethionamide in Bedaquiline-containing regimens.[5] Others suggest there is no benefit from the inclusion of ethionamide in second-line treatment regimens for patients infected with InhA mutations as it confers cross-resistance.[2] In our cohort, the majority had both katG and InhA mutation,[3] making selection of second-line agents challenging.

Overall, 65% of new cases had RR in this study, which is indicative of community transmission. The implication of high rates of primary infection in this region coupled with inadequately treated TB or previously untreated DR-TB can provide the conditions for future transmission.[3] The introduction of short course TB treatment regimens in PNG in 1989 may have been beneficial to improve compliance and thus reduce the likelihood of a drug-resistant foothold.[7] However, without fixed dose combinations, agents can be used separately and some of the drugs used to treat TB (predominantly rifampicin) may have been commonly used in general medicine in PNG as has been observed elsewhere[8] increasing the risk of resistance amplification. Until 2012, DR-TB diagnostic capability was not available on Daru Island and, hence, health professionals on Daru Island and in the Treaty villages of PNG were unaware of the evolving DR-TB situation. In 2004, the WHO recommended that treatment for MDR-TB only occur in TB programmes that were successfully managing their DS-TB cases; however,

as health services on Daru Island were not aware of the presence of DR-TB the region until 2008, their MDR-TB crisis was left to deepen unabated.

Treatment was available for PNG national patients diagnosed with DR-TB in the Torres Strait via Australian outreach TB clinical services. As a large proportion of cases diagnosed with DR-TB in this study had been previously treated for TB, it is possible that some were inadequately treated on Daru Island with first-line TB regimens and resistance was acquired during treatment. This is in addition to evidence previously published that many PNG nationals may have received inadequate or incomplete treatment in the Torres Strait between 2000 and 2014.[9]

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Figure 4.2 Torres and Cape TB Control Unit outreach (Foster, 2017)

4.2 Cross-border tuberculosis: opportunities, challenges and change

4.2.1 Aim

1. Explore drug-resistant TB diagnosed in the Torres Strait between 2000 and 2020

In this chapter, I respond to an article written by Baird et al., 2018.[1] I provide context to the Torres Strait / Papua New Guinea (PNG) cross border region and describe some of the difficulties faced by TB control units when managing cross border patients with multidrug-resistant TB. I outline issues faced by residents of PNG requiring ongoing TB care and describe recent improvements in TB management within the PNG Health System. I use information collected from the Torres and Cape Tuberculosis Control Unit PNG Management database to highlight the numbers of PNG patients requiring referral from Primary Health Centres in the Torres Strait to the PNG Health System.

4.2.2 Publication Contribution

I was the lead author of the following published response to Baird et al., 2018.[1] My contribution to the paper was as follows:

- I wrote the ethics and site-specific authorisation applications to use data for this paper.
- I contributed to the design of this paper.
- I collected some data used in this paper.
- I was the lead author of this paper which I initially drafted.
- I shared the manuscript with co-authors to review, edit and contribute to.
- I managed the submission of this manuscript which was accepted for publication.

1. Baird T, Donnan, E., Coulter, C., Simpson, G., Konstantinos, A., Eather, G. Multidrug-resistant tuberculosis in Queensland, Australia: an ongoing cross-border challenge. *Int J Tuberc Lung Dis.* 2018;22(2):206-11.

In reply

We thank Dr Barreto and colleagues for their remarks and would like to respond as follows. We did not use an inventory study to measure underreporting in our study.[1] As we clearly stated in the introduction: '. . . there is no individual TB case notification form in Cape Verde, and the National Programme for the Fight against Tuberculosis and Leprosy (NPFTL) has only aggregated TB data, thus preventing the use of deterministic record linkage to under-reporting assessment.'[1] To perform an inventory study it is necessary to have individual national-level information.[2] Due to the absence of exact identifiers we used probabilistic linkage.

Regarding the case definitions, both Brazilian and World Health Organization (WHO) guidelines on inventory studies consider cases with confirmed or suspected TB as TB cases.[2,3] Our criteria for TB validation are consistent with WHO inventory studies. For the purposes of our study, validated cases were: '1) confirmed, if the bacteriological result was positive; 2) likely if radiographic findings were compatible with TB.' If we considered individuals with characteristic clinical signs only as validated TB cases, the underreporting would be even higher.

In Praia's central hospital we excluded all individuals whose address was not in the research area. At the hospital laboratory, we excluded patients whose address was outside the research area and individuals coming from health units outside Praia county. We assumed that the remaining cases were people residing in Praia. The availability of only partial data on residence in the hospital laboratory represents one of several weaknesses of TB surveillance identified in Praia.

The duplications cited in paragraph 3 of Barreto et al.'s letter did not include data from the National TB registry. The removal considered three data sources: health centres, hospital, and laboratory. These data were linked and the duplications removed. Finally, the number of TB cases diagnosed during the period that was supposed to be notified was compared with the number of cases from the NPFTL registry.

One of the authors of our study has extensive experience in the field of TB and made significant contributions to improving TB surveillance in Brazil.[4] Moreover, we complied with all protocols to ensure the reliability of the data. First, we invited relevant people in Praia working in TB, including the NPFTL team, to discuss their research and to give their contribution. Unfortunately, the director of NPFTL could not attend the meeting. Epidemiologists, statisticians, and physicians present at the meeting recognized the relevance of the data collected and gave their support to the research. Second, we took great care from data collection to analysis, interpretation of results, training of all staff and processing, with double entry of data.

In our analysis, the record linkage process did not impact negatively on our results. However, underestimation of results is prone to occur, as we could not access data on TB patients from the private health system and could not obtain data on patients who died from TB.

The cases of tuberculosis diagnosed prior to 2009 (the inauguration year of the health units) were considered in this study because retroactive reporting is an important surveillance activity. We included those patients who were treated in the Tira-Chapeu and Achada Grande Trás units according to observations in loco. The process of decentralization of TB surveillance in Cape Verde occurred during this period when these health units would report cases.

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Conflicts of interest: none declared.

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Cross-border tuberculosis: opportunities, challenges and change

The issue of multidrug-resistant tuberculosis (MDR-TB) in the Australia/Papua New Guinea (PNG) cross-border region is an example of international health security at its most proximate and urgent. Since 2008, MDR-TB has been known to account for 25% of new cases of TB in the border region.[1] Baird et al. found that 76% of Queensland's diagnosed MDR-TB patients were cross-border PNG nationals.[2]

Traditional inhabitants who reside in the PNG villages closest to the Australian border frequently enter Australia; this is permitted under the Torres Strait Treaty, an exemption from usual visa requirements, including health checks. The absence of

standardised border health checks and the lack of targeted screening in villages means that PNG visitors have fewer diagnostic opportunities, thus potentially increasing the reservoir of infection in communities. Annual visits from PNG nationals into the Torres Strait number 50 000,[3] raising the risk of transnational spread of MDR-TB.

Providing care for patients with MDR-TB raises challenges for any organisational unit. It requires supervised therapy, monitoring, adequate drug supply and robust logistics to ensure that second-line treatment of MDR-TB can be used safely and patients are retained in care. The difficulties of managing MDR-TB across an international border is reflected in the report by Baird et al.[2] Under Queensland Health's care, only 45.8% of cross-border patients received any injectable agent due to logistical problems, and only 31.5% of the complete cohort had a successful outcome.[2]

In 2012, Queensland Health closed the Saibai and Boigu TB outreach clinics, with a revised aim to recognise and refer patients back to the PNG health care system at Daru General Hospital (DGH), which has donor support from the Australian Government and political commitment on both sides of the border. This, too, has its constraints and risks, and accessing reports on programme outcomes can be difficult. Daru is not easy to access and referred patients may not present due to prohibitive travel costs, limited family support on Daru, no accommodation options or fear of stigma or violence.

Nevertheless, preliminary results suggest an improvement in treatment success reported in 61.2% of drug-resistant patients managed on Daru in a 2012 cohort,[4] and this is reported to be steadily improving. The Daru TB Programme now provides DOTS-Plus for MDR-TB patients, community treatment sites and supporters and onsite diagnostic facilities.[5] Furthermore, DR-TB case detection in children has improved after training clinicians in fine needle and gastric aspiration.[4]

The implementation of a TB Unit based in the Torres Strait since 2016 has allowed for rapid and streamlined transfer and decision making, improved processes to protect residents of the Torres Strait and improved logistics and communication with Daru. With 21 cross-border TB patients referred from the Torres and Cape TB Unit to DGH in 2016–2017, the system's success will depend on rapid transfer to Daru for treatment, high levels of retention in care and greater transparency of outcomes and results. Each of these in turn depends on a resilient and inclusive health system in PNG.

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Conflicts of interest: none declared.

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An opportunity to compare the effects of BCG-Moreau and BCG-Russia in Brazil

Most bacilli Calmette-Guérin (BCG) supplied by UNICEF to low-income countries is made from seed-strains of BCG-Russia, but BCG-Russia may be much less effective than BCG-Denmark and BCG-Japan.[1] If this is true, very substantial improvements in child health could be achieved by simply changing the strains of BCG used for routine immunisation. The World Health Organization has recently emphasised the need for more studies of the clinical effectiveness of different strains of BCG.[2,3]

In 2000, Comstock suggested that protection against tuberculosis could be tested with an ABAB cohort study, in which neonates in a region would be vaccinated with one strain (A) of BCG for a year, a

Figure 4.3 PNG women sells their handicrafts at the markets on Saibai Island (Foster, 2017)

4.3 Time to commencement of effective treatment in patients with drug-resistant tuberculosis diagnosed in the Torres Strait / Papua New Guinea cross-border region

4.3.1 Aims

2. Explore drug-resistant TB diagnosed in the Torres Strait between 2000 and 2020.
4. Determine time to treat using comparison of median delays and selected variables that contribute to total time to treat via Time to Event analyses.
5. Identify variables that contributed to excessive delays in the diagnostic and treatment pathway.

In this paper, I determine the time (in days) from onset of TB-related symptoms to commencement of effective TB treatment in DR-TB patients diagnosed in the Torres Strait between 2000 and 2020. I identify the overall median time to treat, and compare the median time to treat across all diagnostic year groups which reflect changes to clinical practice over time. I analyse the impact of case type (new versus previously treated) on treatment delays. I compare the total time to treat and the implementation of advanced diagnostic technology which was introduced in Queensland in November 2010. Outputs of the analyses are that 1) the establishment of a locally-based TB Control Unit has significantly reduced the time from onset of symptoms of effective TB treatment commencement for DR-TB cases diagnosed; 2) new DR-TB cases are associated with reduced treatment delay, when compared with previously treated cases and 3) advanced diagnostic technology helped to reduce the time from onset of symptoms to effective TB treatment commencement.

4.3.2 Publication Contribution

I was the lead author of the following peer-reviewed paper. My contribution to the study and subsequent outputs were as follows:

- I developed the concept for this study.
- I contributed to the design of this study.
- I wrote the ethics and site-specific authorisation applications and obtained clearance to use data for this paper.

- I wrote the Public Health Act authorisation application and obtained clearance to access data for this paper.
- I collected the data for this study.
- I attended a number of workshops about how to conduct quantitative research via the Doctoral Cohort Program at JCU.
- I used Excel and SPSS to organise the data collected and attended to all coding.
- I conducted the analysis with results reviewed by my supervisory team.
- I was the lead author of the manuscript which I initially drafted.
- I managed the submission of this manuscript which was peer-reviewed and accepted for publication.
- I prepared various presentations that included the results from this study for the Torres and Cape Hospital and Health Service Board – Safety & Quality Committee (29.04.21); Queensland Health Directors of Clinical Governance Implementation and Improvement Partnership (11.06.21) and the National Tuberculosis Advisory Committee (22.06.21).

4.3.3 Translation Research

- I met with the Acting Executive Director Medical Services of the Torres and Cape Hospital and Health Service to discuss the findings of the study. I have received in-principle approval to implement advanced diagnostic technology locally at Thursday Island Hospital in the Torres Strait. (Xpert for TB diagnostics became available in the Torres Strait in 2023).

Results from this study are included in the following peer-reviewed publication.

Rural and Remote Health rrh.org.au
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ORIGINAL RESEARCH

Time to commencement of effective treatment in patients with drug-resistant tuberculosis diagnosed in the Torres Strait-Papua New Guinea cross-border region

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ABSTRACT:

Introduction: Delays between self-reported symptom onset and commencement of effective treatment contribute to ongoing tuberculosis (TB) transmission, which is a particular concern in patients with drug-resistant (DR)-TB. The study authors assessed improvements in time to commencement of effective treatment in patients diagnosed with DR-TB in the Torres Strait–Papua New Guinea cross-border region.
Methods: All laboratory-confirmed DR-TB cases diagnosed in the Torres Strait between 1 March 2000 and 31 March 2020 were reviewed. Total time from self-reported onset of symptoms to effective treatment commencement in different programmatic time periods was assessed. Pairwise analyses and time to event proportional hazard calculations were used to explore the association between delays in median time to effective treatment, and selected variables. Data were further analysed to examine predictors of excessive treatment delay.
Results: The median number of days from self-reported onset of symptoms to effective treatment commencement was 124 days (interquartile range 51–214) over two decades. Between 2006 and 2012, most (57%) cases exceeded this 'grand median' while the median 'time to treat' in the most recent time period (2016–2020) was significantly reduced to 29 days ($p<0.001$). Although there was a reduction in the median 'time to treat' with the introduction of Xpert MTB/RIF (135 days pre-Xpert v 67 days post-Xpert) this was not statistically significant ($p=0.07$). Establishment of the Torres and Cape TB Control Unit on Thursday Island (2016–2020) was significantly associated with reduced treatment delay, compared to the previous TB program period (2000–2005, $p<0.04$; 2006–2012, $p<0.001$).
Conclusion: Minimising TB treatment delay in remote settings like the Torres Strait–Papua New Guinea cross-border region requires effective decentralised diagnosis and management structures. The results of this study suggest that the establishment of the Torres and Cape TB Control Unit on Thursday Island significantly improved time to commencement of effective TB treatment. Possible contributing factors include better TB education, cross-border communication and patient-centred care.

Keywords:

cross-border, drug-resistant tuberculosis, time to treat, Torres Strait.

FULL ARTICLE:

Introduction

Tuberculosis (TB) remains a disease of public health significance, with an estimated 10 million cases diagnosed in 2019[1]. Australia's TB incidence is considered low at 5.5/100 000 population[2]; however, TB disproportionately affects Indigenous Australian populations, and the incidence rate in the Torres Strait in 2014 was 107/100 000 population (based on 2011 Census population data). In Papua New Guinea (PNG), TB is the leading cause of death from an infectious agent, with a TB case notification rate of 674/100 000 population in the Western Province in 2016[3]. In 2014, the PNG National Department of Health declared Daru Island in the Western Province a 'hot-spot' – of approximately 500 cases of TB diagnosed on the island each year, one in ten TB cases were multidrug-resistant (MDR)[4].

Disease control is impeded when DR-TB is poorly managed. DR-TB can be community-acquired or be the result of irregular or interrupted treatment, inadequate drug regimens or malabsorption of medication[5,6]. Most types of DR-TB, including rifampicin-resistant (RR) and MDR-TB, require second-line drugs to treat; these are more expensive, toxic, and the length of treatment is time-consuming[7]. MDR-TB is TB that is resistant to both isoniazid and rifampicin, two of the most potent TB drugs[8]. Two major factors of treatment success for DR-TB patients are prompt diagnosis and commencement of effective sustained treatment[6]. Delays in treatment commencement can result in high bacillary load with increased infectiousness and spread[9]. Early effective treatment reduces the bacterial burden and limits transmission[8].

The Australian National TB Advisory Committee considers time to effective treatment commencement to be one of the most important markers of effective TB control programs[10]. In settings with excessive delays from symptom onset to treatment commencement, higher drug resistance is expected[11]. Currently, there is no global consensus on how to define excessive delay from self-reported symptom onset to treatment commencement. In principle it is important to minimise treatment delay to limit transmission risk[12,13]. Patient factors such as reduced health-seeking behaviours due to poor knowledge, distrust or other impediments may delay presentation[13,14]. Factors related to the health system such as poor TB awareness by staff, or a lack of appropriate laboratory facilities, as well as radiology and treatment access, can also contribute to treatment delay[14,15]. Individual and health system related factors that lead to delays should be monitored and addressed by TB control units[10].

Geographical and geopolitical challenges in the Torres Strait–PNG region create healthcare disparities that affect diagnosis, referral pathways, treatment and management of TB patients in the Torres Strait Protected Zone (TSPZ). Since the ratification of the Torres Strait Treaty in 1985, free bidirectional movement has been allowed for traditional, family, economic and trade purposes in the TSPZ between 13 PNG Treaty villages in the Western Province and 13 adjacent Australian Torres Strait Islands[16,17]. As a result of this international agreement, TB has often been able to move, unhindered, across borders[18]. Primary transmission of TB and

the rise of drug resistance are cause for concern for at-risk Australian and PNG border communities[19]. The Torres Strait Treaty does not include access to Australian healthcare for PNG villagers living adjacent to the Australian border, despite the narrow (4.7 km) stretch of water separating the two countries (Fig1). In response to the urgent nature of some healthcare needs, Queensland Health provides humanitarian aid to those most in need as well as providing triaging and point-of-care diagnostic services.

Optimising models of care for TB patients living in the Torres Strait–PNG international border region has been challenging, and the programmatic TB response in this remote area has evolved over time (Fig2). Although Torres Strait and PNG cross-border communities are subject to a similar TB risk they do not have access to the same level of health care[20]. On the Australian side of the border, high-risk screening and passive TB case finding is standard practice whereby cases are diagnosed post-investigation of TB-related symptoms or incidentally while other medical conditions are being investigated[10,21]. During the study period, PNG nationals requiring TB work-up who did not present to an Australian health facility needed to travel to Daru General Hospital, located at least 2 hours away by small motorised boat (at a cost of A$240)[22]. The region's geography and associated travel costs renders accessing TB health are services prohibitive for PNG nationals residing adjacent to the TSPZ. The Multi-dimensional Poverty Index in the area is estimated to be 0.32[23]. Over the past 20 years, poverty has affected time to treatment commencement for PNG residents with TB living adjacent to the Australian border. The consequences are sustained transmission risk and rapid growth of DR-TB on both sides of the border.

Time from self-reported onset of symptoms to effective treatment commencement has not previously been investigated in this particular context. This study aimed to explore total time from self-reported onset of TB symptoms to effective treatment commencement for all DR-TB cases diagnosed in the Torres Strait–PNG border region over two decades. This study identifies factors associated with the time between self-reported symptom onset to effective treatment commencement as well as discusses programmatic interventions that may have contributed to reduced treatment delays over time. As DR-TB transmission is an established risk in the Torres Strait–PNG border, this study may help to improve programmatic management of TB in the region to the benefit of both Australian and PNG healthcare systems and local communities.

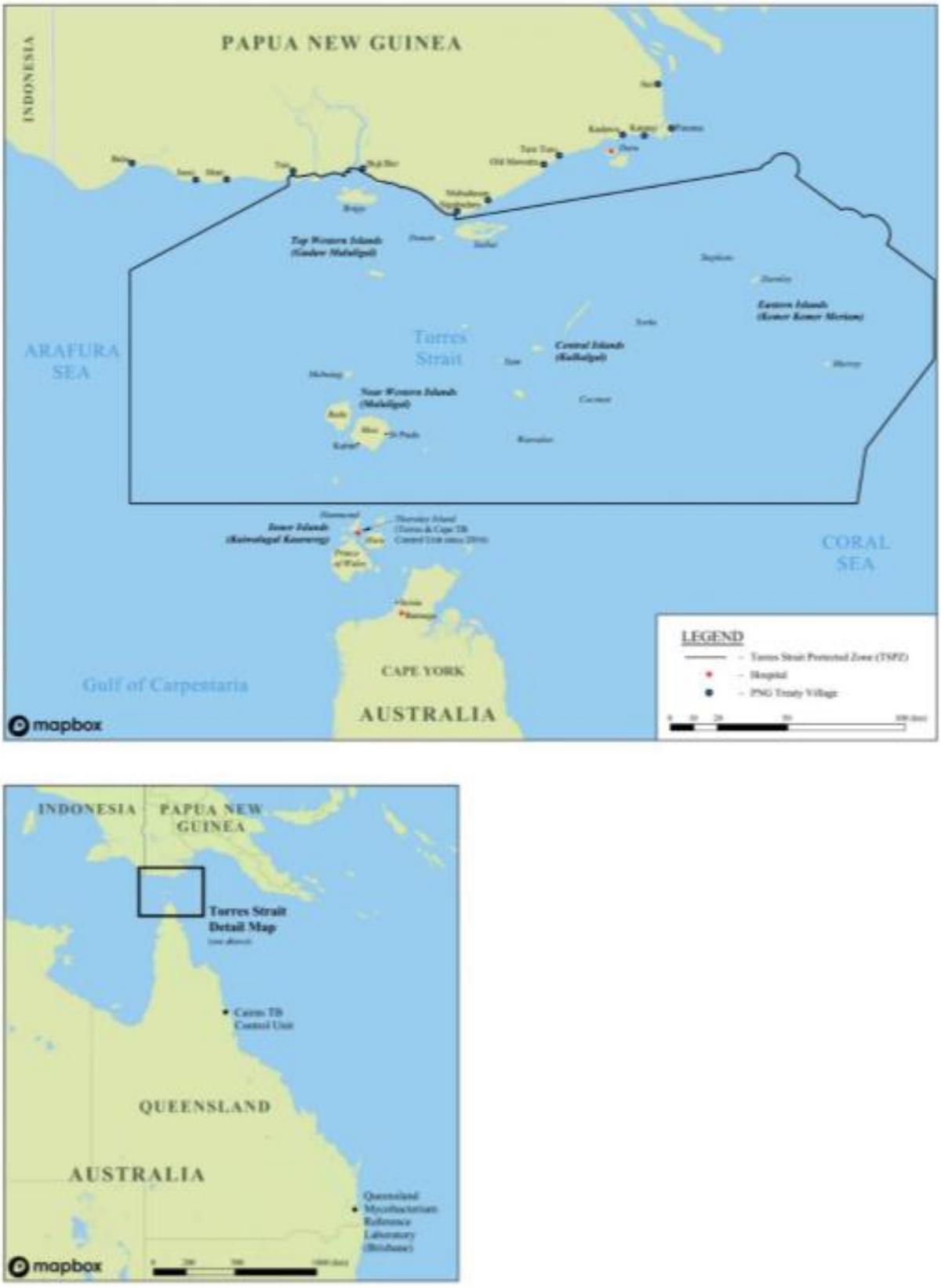


Figure 4.3.1 Map of the Torres Strait/Papua New Guinea cross-border region

Figure 4.3.2 Description of the different tuberculosis programmatic time periods in the Torres Strait/Papua New Guinea cross-border region between 2000 and 2020

Methods

Design and study population

This retrospective cohort study included all patients from Australia or PNG who were diagnosed in the Torres Strait Islands with microbiologically confirmed DR-TB between 1 March 2000 and 31 March 2020. Patients of all ages, including children, were included in the study, as were those with pulmonary, extrapulmonary, smear-negative and smear-positive disease.

Sputum and other histological samples were collected in the Torres Strait Islands and transported via sea and air to a WHO-designated Supranational Reference Laboratory, the Queensland Mycobacterium Reference Laboratory (QMRL)[24] (Fig1). Confirmation of DR-TB diagnosis was confirmed by culture and phenotypic drug susceptibility testing (DST) pre-November 2010, or by Cepheid Xpert® MTB/Rif Assay (Xpert) (rapid diagnostic technology), culture and DST post-November 2010[24].

Definitions

The sample size is based on 133 cases with DR-TB, with 113 experiencing the event (known effective treatment commencement).

Effective treatment was defined as the implementation of appropriate second-line TB treatment for RR/MDR-TB cases and appropriate TB treatment for other drug-resistant cases, whether this was programmatic/empiric or personalised.

Time to event was defined as the sum in days of the following three distinct intervals:

1. patient delay: time from self-reported TB symptom onset to presentation at a health facility in the Torres Strait
2. health system delay: time from presentation at a health facility to being diagnosed with TB
3. treatment delay: time from diagnosis to event – effective treatment commencement.

As not all participants commenced treatment, the data are right-censored. The 20 censored cases that were transferred out or died were observed in the study to pass through the sum (in days) of patient delay and health system delay – time from self-reported onset of symptoms to diagnosis.

Diagnosis year group reflects the changes in programmatic TB responses in the remote Torres Strait–PNG international border that occurred over time (Fig2).

Case type was defined as either a new case, or relapsed case following full or partial treatment in Australia or overseas. These cases were analysed as independent events. Four patients who had previously received full or partial treatment were diagnosed twice in this study, and were counted discretely as separate events. Self-reported onset of symptoms did not overlap for any of these four patients.

Data collection

Clinical and demographic data were sourced from the Queensland Notifiable Conditions System (NoCS), and drug resistance for each case was verified in Queensland Health's laboratory results software, AUSLAB. Case notifications were cross-checked between NoCS and AUSLAB, and one case of DR-TB identified from NoCS, but not from AUSLAB, was removed from the study.

The date of symptom onset and treatment commencement in NoCS was cross-checked against self-reported symptom onset date and treatment commencement documented in patient charts, Queensland Health's statewide patient database, The Viewer[25], and in the Torres and Cape Hospital and Health Service (North) patient database, Best Practice[26].

As NoCS relied on retrospective submissions of case notification data throughout the study period, original or copies of handwritten progress notes in patient charts, and referrals and progress reports in The Viewer and Best Practice, were considered the sources of truth for this study for symptom onset and treatment commencement. If this evidence was not available, the date of symptom onset and treatment commencement in NoCS was used.

For data pertaining to 2016 and onwards, a combination of NoCS, The Viewer, Best Practice and two Excel spreadsheets specifically used to manage patient data for residents of the Torres Strait Islands, and PNG patients diagnosed with TB, were used to ascertain self-reported date of onset of symptoms and date of treatment commencement for each case. Prior to the border closures associated with the COVID-19 pandemic, clinicians from the Torres and Cape TB Control Unit met with clinicians from the Daru TB Programme to discuss treatment commencement dates and treatment outcomes of shared cross-border patients. Further, a core component of the Torres and Cape TB Control Unit's cross-border TB portfolio was to share new laboratory results, chest X-ray reports and household contact information with the Daru TB Programme.

Patients diagnosed with DR-TB at an Australian health facility prior to the end of 2012 commenced treatment for DR-TB in Australia because second-line drugs used to treat DR-TB were not yet available on Daru Island. Once drug-susceptibility testing and effective treatment of DR-TB were available on Daru Island, the numbers of DR-TB cases diagnosed by Australian health facilities decreased. Most patients from PNG who were diagnosed at Australian health facilities with DR-TB between 2013 and 2020 commenced treatment in PNG; however, the most critically unwell, who were transferred to either Thursday Island, Cairns or Townsville Hospitals may have commenced treatment in Australia. Data pertaining to the site at which each patient commenced effective treatment were not collected.

Data analyses

All statistical analyses were performed using SPSS v27 (IBM; http://www.spss.com).

Frequencies and percentages were calculated for categorical variables including treatment event (effective treatment commencement or transfer out/death), visa status, case type, RR-TB, MDR-TB and gender.

Tests for normality were performed for mean, median, skewness and kurtosis, and visual inspections of histograms were reviewed. Assumptions for normality were violated and data were not normally distributed. Medians and interquartile ranges (IQR) were used for data that were not normally distributed to demonstrate differences in the total time to effective treatment commencement across the four different time periods. When determining median days to effective treatment commencement, patients who did not commence known treatment, and were transferred out or died, were removed from analyses – hence time to treatment outcomes should be interpreted as conditional on treatment commencement.

To determine any association between advanced diagnostic technology implementation in Queensland from November 2010, a non-parametric independent samples Median Test for *k* samples was used. The dependent variable was total time in days to known treatment commencement and the independent categorical variables were pre and post-Xpert. Patients who did not commence effective TB treatment due to death or transfer out were removed from the analyses.

Independent samples median test of frequencies was used to identify the grand median, and to demonstrate frequencies above and below the median days to effective treatment commencement across different time periods. Post-hoc analyses were performed using pairwise comparison to determine the differences of median delays across the four different time periods, reflecting different programmatic management types. The dependent variable was total time to event (symptom onset to effective treatment commencement), and two time periods were compared at a time using pairwise comparison. Statistical significance was set at $p<0.05$. Due to the relatively small sample size and to counter a potential type 1 error that may occur when multiple analyses are performed on the same dependent variable, a Bonferri correction was applied[27]. The alpha was lowered by taking the unadjusted *p*-value and multiplying it by the number of pairwise comparisons[27].

A Cox proportional hazards regression plot was used to illustrate the time to known treatment commencement in days, stratified by case type (new versus previous full or partial treatment).

Ethics approval

This study was conducted with ethics approval from the Far North Queensland Human Research Ethics Committee (HREC) (HREC/17/QCH/74-1157), the Chair of James Cook University HREC (H7380) and a Public Health Act approval (QCH/36155 – 1157).

Results

Descriptive statistics

Table 1 shows that of 133 patients diagnosed with DR-TB between 2000 and 2020, 20% had previously received full or partial TB treatment in Australia or overseas and 70% were RR. The proportion of patients with MDR-TB overall who previously received full or partial treatment was 26% (23/89 cases). Between 2000 and 2005, 100% of DR-TB cases were new and, of those, 71% were RR.

Table 2 shows that the median time to effective treatment commencement for 113 patients increased after 2000–2005 (92 days; IQR 70–201) and peaked between 2006 and 2012 at 138 days (IQR 72–251). Reduction to 29 days (IQR 7–45) was observed between 2016 and 2020.

Table 4.3.1 Characteristics of drug-resistant tuberculosis patients diagnosed during different programmatic time period in the Torres Strait / Papua New Guinea cross-border region between 2000 and 2020

Characteristic	All cases 2000–2020 (*n*=133)	2000–2005 (*n*=14)	2006–2012 (*n*=96)	2013–2015 (*n*=11)	2016–2020 (*n*=12)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Treatment group					
Transfer out or death	20 (15)	2 (14)	12 (13)	5 (46)	1 (8)
Treatment commenced	113 (85)	12 (86)	84 (88)	6 (55)	11 (92)
Visa status					
Australian resident	9 (7)	0 (0)	2 (2)	4 (36)	3 (25)
PNG non-Treaty visitor	38 (29)	5 (36)	28 (29)	1 (9)	4 (33)
PNG Treaty visitor	86 (65)	9 (64)	66 (69)	6 (55)	5 (42)
Case type					
New case	107 (81)	14 (100)	72 (75)	10 (91)	11 (92)
Full or partial treatment overseas	21 (16)	0 (0)	20 (21)	0 (0)	1 (8)
Full or partial treatment Australia	5 (4)	0 (0)	4 (4)	1 (9)	0 (0)
Rifampicin resistance					
Not RR	40 (30)	4 (29)	34 (35)	1 (9)	1 (8)
RR	93 (70)	10 (71)	62 (65)	10 (91)	11 (92)
Gender					
Male	58 (44)	6 (43)	44 (46)	3 (27)	5 (42)
Female	75 (56)	8 (57)	52 (54)	8 (73)	7 (58)
Multidrug-resistant TB	(*n*=93)	(*n*=10)	(*n*=62)	(*n*=10)	(*n*=11)
Previous full or partial treatment	23 (25)	0 (0)	21 (34)	1 (10)	1 (9)
New case	70 (75)	10 (100)	41 (66)	9 (90)	10 (91)

PNG, Papua New Guinea. RR, rifampicin resistant. TB, tuberculosis.

Table 4.3.2 Time to commencement of effective drug-resistant tuberculosis treatment across different tuberculosis programmatic time periods in the Torres Strait/Papua New Guinea cross-border region between 2000 and 2020

Variable	Time period†			
	Services coordinated from Cairns			Thursday Island coordination
	2000–2005	2006–2012	2013–2015	2016–2020
n	12	84	6	11
Median (IQR)	92 (70–201)	138 (72–251)	67 (46–198)	29 (7–45)

† See Figure 2 for description of tuberculosis programmatic time periods in Torres Strait–Papua New Guinea cross-border region, 2000–2020
IQR, interquartile range.

Inferential statistics

The independent samples median test (Fig3) shows that the grand median time from self-reported TB symptom onset to known effective treatment commencement for DR-TB cases was 124 days (IQR 51–214). Figure 3 shows post-hoc pairwise analyses demonstrating a statistically significant difference between the 'time to known effective treatment commencement' medians of patients in the diagnosis year groups 2000–2005 and 2016–2020 (p=0.04), and year groups 2006–2012 and 2016–2020 (p<0.001). Frequencies of cases both above and below the median are illustrated in Figure 3. Fifty-seven percent (n=48) of cases diagnosed between 2006 and 2012 exceeded the median total time to effective treatment commencement. All other diagnosis year groups had greater numbers of participants below the median than above the median.

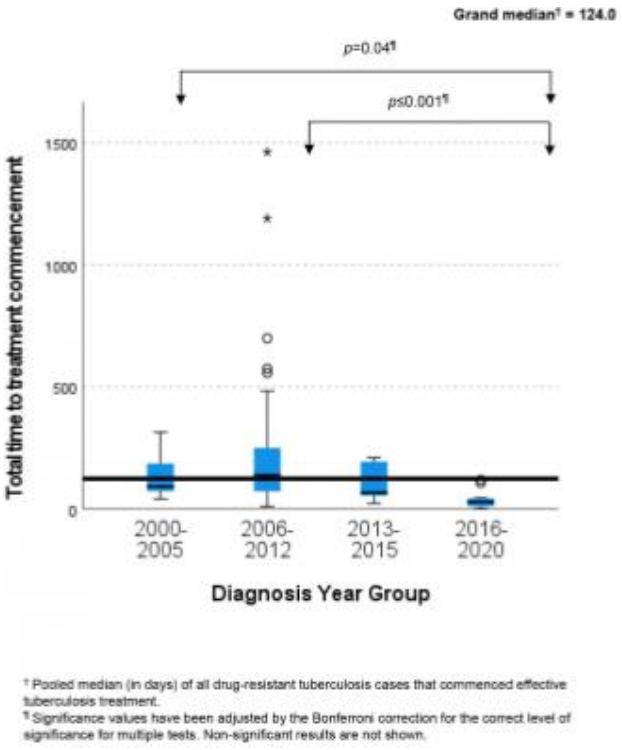
The independent samples median test (Table 3) demonstrates that post-implementation of the rapid diagnostic technology, Xpert, the median time from self-reported symptom onset to treatment commencement was 67 days (IQR 30–202) and the pre-Xpert time to treat median was 135 days (IQR 73–248; p=0.07).

Figure 4a shows the Cox proportional hazard plot for case type and total time to commencement of effective treatment. As can be seen in this figure, patients who had previously received full or partial treatment demonstrated a more gradual slope to hazard (ie 'time to known commencement of effective treatment'). Case type emerged as a predictor of earlier effective treatment commencement (hazard ratio = 0.6 (95% confidence interval (CI) 0.35–0.89); p=0.01). Figure 4b shows the Cox proportional hazard plot for TB services provided by Cairns TB Control Unit and the Torres and Cape TB Control Unit. This figure shows that patients treated within the Cairns TB Control Unit demonstrated a more gradual slope to hazard (ie 'time to known commencement of effective treatment').

Table 4.3.3 Time to commencement of effective drug-resistant tuberculosis treatment pre and post-Xpert availability in the Torres Strait/Papua New Guinea cross-border region between 2000 and 2020

Variable	Pre-Xpert† (2000 – Oct 2010)	Post-Xpert (Nov 2010 – 2020)	*p*-value
n	75	38	
Median (IQR)	135 (73–248)	67 (30–202)	0.07

† Xpert® MTB/RIF assay was performed in Cairns or Brisbane.
IQR, interquartile range.



[1] Pooled median (in days) of all drug-resistant tuberculosis cases that commenced effective tuberculosis treatment.
[1] Significance values have been adjusted by the Bonferroni correction for the correct level of significance for multiple tests. Non-significant results are not shown.

Figure 4.3.3 Variability in median time to treatment commencement across different tuberculosis programmatic time periods in the Torres Strait/Papua New Guinea cross border region between 2000 and 2020

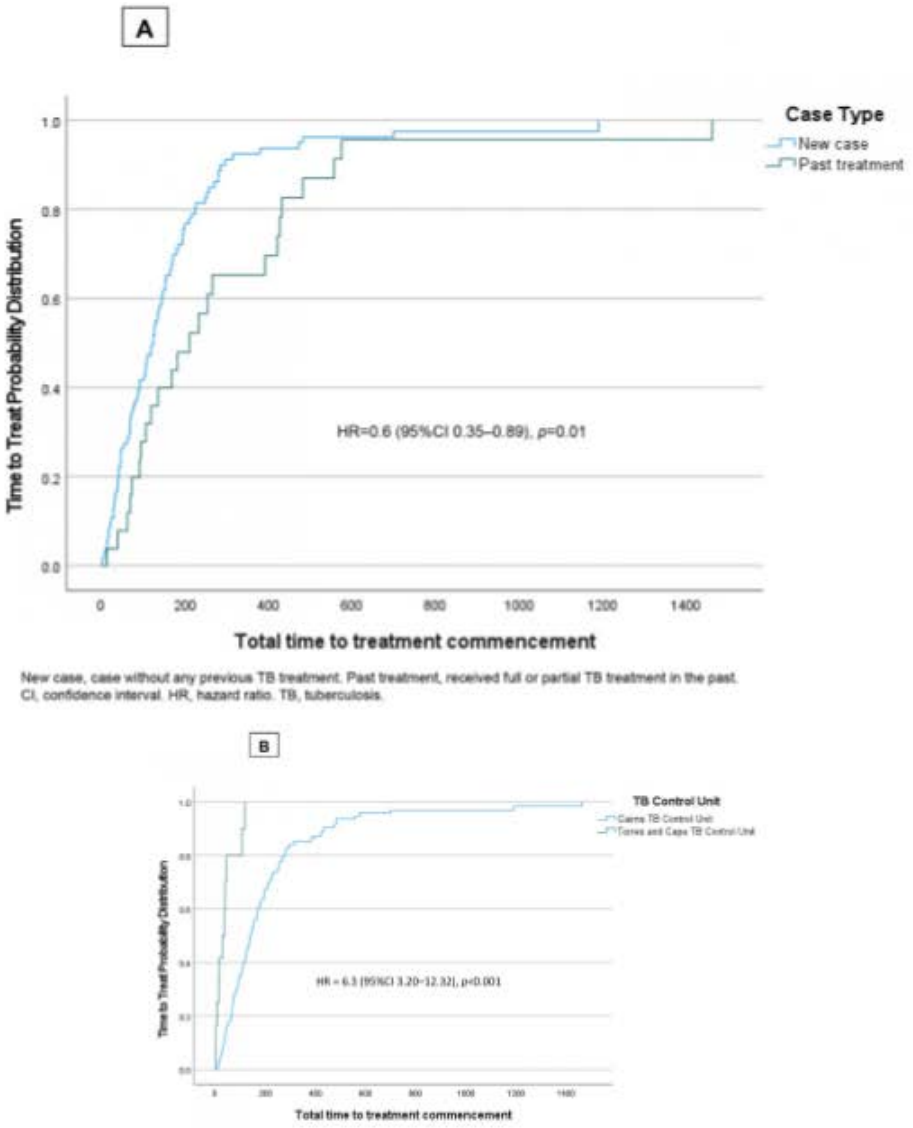


Figure 4.3.3 (a) Time to treat (days) stratified by 'new case' and 'past treatment' in the Torres Strait/Papua New Guinea cross border region between 2000 and 2020; (b) Time to treat (days) stratified by TB services provided by the 'Cairns Tuberculosis Control Unit and Torres and Cape Tuberculosis Control Unit' in the Torres Strait/Papua New Guinea cross border region between 2000 and 2020

Discussion

In this study, the lengthy median delay from self-reported onset of symptoms to effective treatment commencement was 124 days (IQR 51–214) over the study period. This is approximately four times more than the time to treat in a study conducted in the late 1990s in metropolitan Victoria, Australia, where 33 days from symptom onset to treatment commencement was deemed an acceptable delay[28]. Even considering remoteness, this key finding is still well above delays in other similar settings, and the present study authors offer 4–6 weeks as an acceptable delay, based on results from Australian literature. A systematic review of 198 studies reported a pooled mean total delay of 88 days across low- and middle-income countries in both urban and remote settings[12]. Remoteness of the region, diagnostic services located on mainland Australia, access to pharmaceuticals for patients who commenced treatment in Australia and limited telecommunications with residents of Treaty and non-Treaty villages in PNG all remained unchanged throughout the study period, therefore variation of time to effective treatment is likely to be associated with other factors. These may be low level of health service coverage and lack of awareness of TB, as previously identified in other rural and remote settings[14].

Excessive delays between onset of symptoms and effective treatment commencement may contribute to ongoing transmission of TB in the region[15], hence various programmatic initiatives were introduced by the Torres and Cape TB Control Unit to strive to reduce this time. For example, culturally competent health promotion has been shown to increase knowledge and uptake of disease-prevention strategies in culturally diverse communities[29]. Initiatives introduced by the Torres and Cape TB Control Unit included specific onboarding and opportunistic education for staff, and development and distribution of linguistically and culturally appropriate TB education materials. These initiatives may have been contributing factors to the decrease in time to

effective treatment (29 days) from 2016 to below the level considered acceptable in metropolitan Victoria (33 days)[28]. These contributing factors may require further investigation to better understand their effect on time to treatment.

Changes to the management of TB in the region over time may help to explain a near five-fold decrease in the median time to treat between 2006 to 2012 and 2016 to 2020. By 2012, the Daru TB Program in PNG, supported by the Australian Government, had developed capacity to manage both fully susceptible and DR-TB cases[22]. Measures introduced in the region from 2014 and programmatic changes from 2016 may have also contributed to a reduction in median time from onset of symptoms to effective treatment commencement. In 2014-2016, Australian Government funding supported the delivery of TB-clinician-led initiatives to enhance TB knowledge among local communities and healthcare facilities on both sides of the international border[20,30-32]. This enhanced knowledge of the basic features of TB may have assisted in reducing the time from self-reported onset of symptoms to presentation at a health facility.

During this time, Australian Government funding also supported a data integrity project[33] to gather all historic PNG patient charts located on Australian Torres Strait Islands and patient data contained in an electronic medical record used prior to 2011: Holt's database[26]. Data migration into best-practice software enabled clinicians to access patient information in a single electronic database. As a result of the cross-border data integrity project, from 2015 all PNG nationals presenting with signs and symptoms of TB to a primary health centre (PHC) in the TSPZ have an electronic medical record. This initiative led to increased real-time visibility of all patients in the TB care pathway, provided access to information about past TB diagnoses and past contact history dating back to the 1950s, and allowed for identification and follow-up of previously treated cases.

Notably, the absence of advanced diagnostic technology such as Cepheid Xpert® MTB/Rif Assay, which can identify RR in less than 2 hours, can add considerable time to health system related delays[34]. Implementation of Xpert in Queensland, Australia in November 2010 improved the overall median delay to 67 days in this study, which was approximately half the median pre-Xpert, indicating that implementation of Xpert in the Torres Strait may have helped to further reduce time to effective treatment delays[35]. Although the point-estimate difference pre- and post-Xpert was large, there were additional temporal trends at the time and the difference pre- and post-Xpert was not statistically significant in this study.

Outreach TB specialist services provided by staff based in Cairns prior to 2016 may have influenced time to treatment commencement. Logistical issues and inclement weather at times affected the ability for Cairns-based TB clinicians to access the Torres Strait to review patients and commence them on treatment[22]. In contrast, the Torres and Cape TB Control Unit established in 2016 hosts an ongoing presence of TB clinicians based in the Torres Strait and allowed for a continual service where suspected case management and treatment commencement could occur at any time.

In international border settings, strength is found in collaboration between international partners and where well-defined data sharing and referral agreements are in place[36]. In collaboration with the Daru TB Program, the Torres and Cape TB Control Unit implemented new procedures to enhance recognition and streamline management of symptomatic patients[37]. As a result of improved cross-border communication, programmatic rules and strategies were implemented from 2016 to strive for safe and ethical management of shared and referred patients. These included ensuring Daru's readiness to receive patients discharged from Australian hospitals, timely notification of microbiological and radiological results, an agreement regarding case notifications to avoid over-reporting case numbers, and sharing patient outcome data. The strength of this cross-border collaboration is evidenced in this study by known treatment commencement dates of 11 of 12 cases from 2016.

Traditional risk factors for delays from self-reported onset of symptoms to effective treatment commencement in other settings have included limited access to health facilities, rural or remote location, and distance to diagnostics[12,14]. However, in this study, these factors apply to both new and previously treated cases. With few treatment supporters to administer directly observed therapy in most of the PNG Treaty villages[38] and challenging cross-border communication pathways, previous compliance history and assurances of treatment compliance to follow were not always known. It should be emphasised that none of the variables in this study were highly predictive, which shows that there is huge individual patient variation in time to effective treatment commencement and no easily identifiable risk group. It is possible that treatment delays were more prominent in patients who had previously received some treatment due to a lack of information, patient counselling and education from past TB care providers[39]. As previously treated patients may have had negative past treatment experiences, thus delaying retreatment commencement, additional support for these patients is warranted[40].

To help minimise the economic burden and improve timely access for PNG patients receiving TB care in the Torres Strait between 2006 and 2012, the Cairns TB Control Unit initiated free transport for PNG nationals accessing outreach specialist clinics on Saibai and Boigu Islands (Fig1); however, large numbers of patients failed to attend appointments[22]. A previous study identified that of 73 PNG MDR-TB patients diagnosed in the Torres Strait, 15 were lost to follow-up, and a further 25 had an unknown treatment outcome[22]. A recent study conducted on Daru Island reported longer delays to treatment commencement in symptomatic DR-TB household contacts presenting for TB screening when compared to symptomatic drug-susceptible household contacts[41]. This suggests that there may be country-specific risk factors that require focused support for DR-TB patients and their close contacts. It may also indicate that previously treated patients may have reduced access, a reluctance to present or have different ideologies, prompting a need for additional support for this cohort of patients.

Potential reasons for delays in previously treated cases could be that TB patients may not have been aware that they could

be diagnosed twice, may have been too sick to present earlier, or may not have been experiencing any signs and symptoms at all. It is also possible that pain and adverse reactions from injectable drugs used in previous management of DR-TB acted as a deterrent for patients or their close contacts presenting earlier[42], although it should be noted that only 45.8% of MDR-TB cases diagnosed in PNG nationals in this region between 2000 and 2014 received injectables[22]. Nevertheless, as 80% of cases were new in this study, this suggests that there may be evidence of acquired drug resistance in this population as a result of interrupted, irregular or inadequate treatment. Future qualitative research may assist TB programs in the Torres Strait to identify reasons why previously treated cases presented late in this region, and lead to improved and targeted strategies to improve early entry into the TB care pathway.

Limitations

It is possible that extensive delays in treatment commencement were attributed to repeated patient visits to PHCs, serviced by outreach rural generalist practitioners. It is possible that some symptomatic patients did not immediately enter into the TB diagnostic pathway as PHC clinicians and rural generalist practitioners may not have recognised TB as a leading differential diagnosis. As a satellite TB service was provided up until 2016, it is possible that TB clinicians were not notified of all symptomatic patients and rural generalist practitioners prescribed a trial of broad-spectrum antibiotics to first rule out lower respiratory tract infections[43], as has been reported in other studies[40,44]. This study did not explore this possibility.

This study only captured PNG patients diagnosed by health services on the Australian side of the border as it focused on the management of DR-TB by the Australian health system only. A similar study could be conducted from the PNG health system's perspective to capture PNG nationals diagnosed and treated by PNG health services to gain greater understanding of the overall management of DR-TB in this cross-border region. Should a study take place, a greater collaboration and linkage of data between health systems from both sides of the border would enhance the understanding of DR-TB management in the region and help improve programmatic strategies across the border.

Conclusion

Minimising diagnostic and TB treatment delay is a global priority. Managing TB in rural and remote settings requires TB programs to strive for minimal diagnostic delay with early initiation of effective treatment. The introduction of a decentralised TB management and control structure in the Torres Strait contributed to improved service delivery and a reduction in time to effective TB treatment commencement. The study's findings suggest that time to effective treatment commencement can be reduced by improved access to advanced diagnostic technology and implementation of locally based, patient-centred initiatives. Evaluating time to effective treatment as a measure of programmatic efficacy is an important and valuable public health and quality improvement approach.

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Figure 4.4 Saibai Island with Papua New Guinea in the distance (Foster, 2019).

4.4 Predictors of unfavourable outcome in patients diagnosed with drug-resistant tuberculosis in the Torres Strait / Papua New Guinea border region

4.4.1 Aims

2. Explore drug-resistant TB diagnosed in the Torres Strait between 2000 and 2020.
3. Explore factors that contribute to poor outcomes in patients with drug-resistant TB.

In this paper, I determine that the presence of coinfection or a comorbidity upon diagnosis with DR-TB in the Torres Strait Islands between 2000 and 2020 is associated with unfavourable outcome. I identify high rates of abnormal blood results in patients with DR-TB. I analyse the impact of previous exposure to TB for patients diagnosed with DR-TB and treatment outcome. I compare the changes to clinical management of TB in the region over time and analyse the effect on treatment outcome. Outputs of the analyses are that 1) patients living with coinfection or a comorbidity at time of DR-TB diagnosis have an increased frequency of poor outcome; 2) 100% of patients with DR-TB/diabetes and 100% of patients with DR-TB aged ≥61 years died; 3) residents of PNG are more likely to have unfavourable outcomes when compared with residents of the Torres Strait Islands; 4) patients with low lymphocyte count and DR-TB are significantly more likely to have an unfavourable outcome; 5) being a close contact of a known TB case was a protective factor associated with good outcomes and 6) a 50% increase in the chance of a good outcome was observed with each incremental diagnostic year group.

4.4.2 Publication Contribution

I was the lead author of the following peer-reviewed paper. My contribution to the study and subsequent outputs were as follows:

- I developed the concept for this study.
- I contributed to the design of this study.
- I wrote the ethics and site-specific authorisation applications and obtained clearance to use data for this paper.
- I wrote the Public Health Act authorisation application and obtained clearance to access data for this paper.
- I collected the data for this study.

- I attended a number of workshops about how to conduct quantitative research via the Doctoral Cohort Program at JCU.
- I used Excel and SPSS to organise the data collected and attended to all coding.
- I conducted the analysis with results reviewed by my supervisory team.
- I was the lead author of the manuscript which I initially drafted.
- I managed the submission of this manuscript which was peer-reviewed and accepted for publication.
- I prepared various presentations that included the results from this study for the Torres and Cape Hospital and Health Service Board – Safety & Quality Committee (29.04.21); Queensland Health Directors of Clinical Governance Implementation and Improvement Partnership (11.06.21) and the National Tuberculosis Advisory Committee (22.06.21).

4.4.3 Translation Research

- I met with the Torres and Cape Tuberculosis Control Unit and the Executive Director Medical Services to discuss the findings of this study. It was agreed that baseline HIV testing will continue for all patients that present to health facilities in the Torres and Cape Hospital and Health Service with signs and symptoms of TB.
- I met with the Cairns Sexual Health team to discuss the findings of this study. Currently, Cairns Sexual Health team order QuantiFERON Gold Assay for all newly diagnosed HIV patients. It was agreed that sputum or other relevant specimens will be collected for AFB and culture for all HIV patients with signs and symptoms of TB.
- I shared the findings of this study with Nursing Unit Managers and Clinical Nurse Consultants within renal and diabetes services in the Torres and Cape Hospital and Health Service.

Results from this study are included in the following peer-reviewed publication.

PLOS ONE

RESEARCH ARTICLE

Predictors of unfavourable treatment outcome in patients diagnosed with drug-resistant tuberculosis in the Torres Strait / Papua New Guinea border region

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Abstract

Drug-resistant tuberculosis (DR-TB) is an ongoing challenge in the Torres Strait Islands (TSI) / Papua New Guinea (PNG) border region. Treatment success rates have historically been poor for patients diagnosed with DR-TB, leading to increased transmission. This study aimed to identify variables associated with unfavourable outcome in patients diagnosed with DR-TB to inform programmatic improvements. A retrospective study of all DR-TB cases who presented to Australian health facilities in the Torres Strait between 1 March 2000 and 31 March 2020 was performed. This time period covers four distinct TB programmatic approaches which reflect Australian and Queensland Government decisions on TB management in this remote region. Univariate and multivariate predictors of unfavourable outcome were analysed. Unfavourable outcome was defined as lost to follow up, treatment failure and death. Successful outcome was defined as cure and treatment completion. In total, 133 patients with resistance to at least one TB drug were identified. The vast majority (123/133; 92%) of DR-TB patients had pulmonary involvement; and of these, 41% (50/123) had both pulmonary and extrapulmonary TB. Unfavourable outcomes were observed in 29% (39/133) of patients. Patients living with human immunodeficiency virus, renal disease or diabetes (4/133; 4/133; 3/133) had an increased frequency of unfavourable outcome (p <0.05), but the numbers were small. Among all 133 DR-TB patients, 41% had a low lymphocyte count, which was significantly associated with unfavourable outcome (p <0.05). We noted a 50% increase in successful outcomes achieved in the 2016–2020 programmatic period, compared to earlier periods (OR 5.3, 95% Confidence Interval [1.3, 20.4]). Being a close contact of a known TB case was associated with improved outcome. While DR-TB treatment outcomes have improved over time, enhanced surveillance for DR-TB, better

Competing interests: The authors have declared that no competing interests exist.

cross border collaboration and consistent diagnosis and management of comorbidities and other risk factors should further improve patient care and outcomes.

Introduction

Drug resistance poses a major threat to global tuberculosis (TB) control, with nearly half a million of the ten million cases in 2019 estimated to be rifampicin resistant [1]. Drug-resistant (DR)-TB refers to TB strains that are resistant to any of the first-line drugs used to treat fully-susceptible TB, any of the second-line drugs used to treat DR-TB, or are resistant to a combination of these drugs [2]. Inadequate adherence to TB treatment may lead to the development of DR-TB and multidrug-resistant (MDR)-TB; resistant to both isoniazid and rifampicin and substantially more difficult and costly to treat [3]. Treatment outcomes are generally worse for DR-TB cases due to the use of less potent drugs, prolonged treatment regimens, difficult adherence and potential severe drug-related adverse effects [4]. Globally, the average treatment success rate in patients with MDR-TB in 2018 was 59% [5], although this is highly variable across countries (Ukraine– 18.1% [6]; China– 52.2% [7]; Ethiopia– 78.6%) [8].

TB control poses an ongoing public health challenge in the Torres Strait / Papua New Guinea (PNG) region. The challenge is compounded by high levels of DR-TB in the Western Province of PNG and in particular, on Daru Island [9, 10] (Fig 1). In 2016, the estimated incidence rate of TB in PNG was 432 / 100,000 population [WHO, 11]; 674 / 100,000 in the Western Province [12]. By comparison, the incidence rate of TB over the border in Queensland, Australia is 5.5 / 100,000 population [13]. In the Torres Strait Islands, 80% of people identify as Torres Strait Islander Indigenous peoples [14]. Indigenous Australians are disproportionately affected by TB when compared to non-Indigenous Australians [15]. It is important to appreciate that residents from specific islands in the Torres Strait and villages in the Western Province of PNG share an open international border (Fig 1), heightening cross-border TB transmission risk [10].

Management of DR-TB is complex and is often further complicated by comorbidities with other communicable and non-communicable diseases [17]. Patients with TB and comorbidities such as renal impairment, diabetes and human immunodeficiency virus (HIV) are more likely to have unfavourable outcomes and are known causes of TB reactivation [18–20]. While the rise in DR-TB is a global concern, TB programs must consider specific local risk factors and programmatic gaps to ensure better outcomes for patients. These considerations may present important opportunities for TB programmes to meet the challenging END TB targets, aiming to reduce the incidence of TB by 90% before 2035 [21].

The aim of this study was to evaluate variables associated with unfavourable outcome and the impact of programmatic changes to models of TB care over time with treatment outcomes in DR-TB patients diagnosed in the Torres Strait / PNG border region. It is the intention that evidence derived from this study will be carefully considered at a programmatic level to further improve outcomes for patients diagnosed with DR-TB in this context.

Methods

Study design and population

We performed a retrospective cohort study of all patients diagnosed with laboratory-confirmed DR-TB between 2000 and 2020 in the Torres Strait Islands, Australia. Pulmonary, extrapulmonary, smear positive and smear negative cases were included, as well as those with

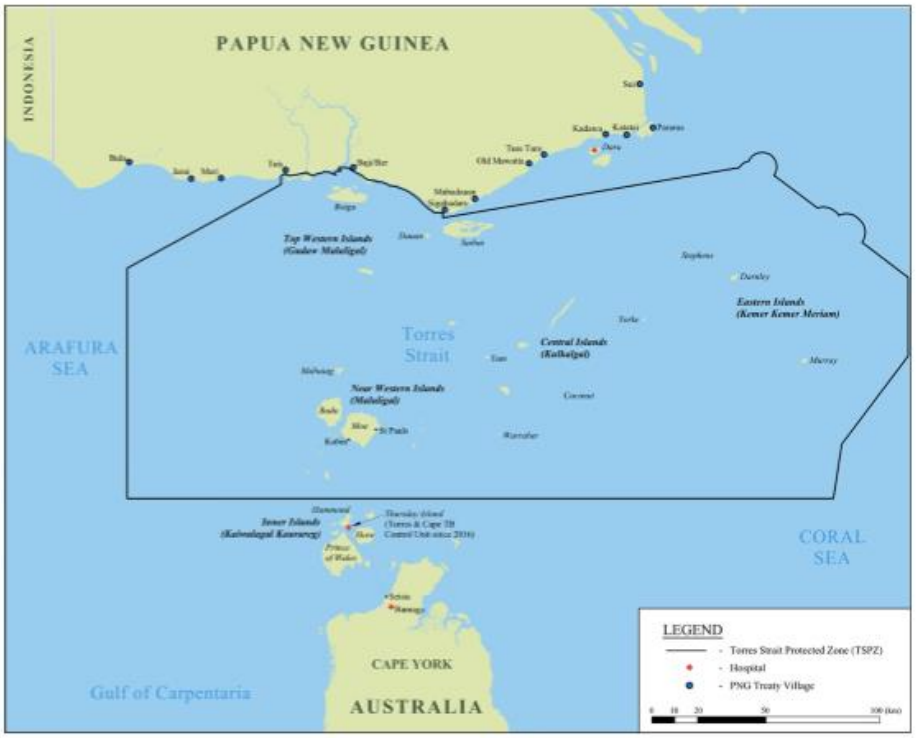

Figure 4.4.1 Map of the Torres Strait/Papua New Guinea cross-border region 16][1] **CC BY 4.0.** [1]International travel without passport or visa is permitted for traditional inhabitants of the Torres Strait Protected Zone and Treaty villages of Papua New Guinea, DOI. 10.6084/m9.figshare.16632823.

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mono (isoniazid, rifampicin or streptomycin mono-resistance), poly (resistant to two or more TB drugs) and MDR-TB (resistant to isoniazid and rifampicin). Streptomycin mono-resistance was included, given the high prevalence reported in parts of PNG [22]. Ethionamide resistance was analysed in relation to MDR-TB cases, given reports of frequent isoniazid and ethionamide co-resistance amongst MDR-TB strains circulating on Daru Island [23, 24].

Patients were excluded from the study if they were residents of PNG villages external to the Western Province of PNG who did not enter the Australian health system via a health facility in the Torres Strait Protected Zone (Fig 1).

Models of TB care–Diagnosis and treatment

There were four models of TB care provided in the region during the study period, over different periods of time (2000–2005; 2006–2012; 2013–2015; 2016–2020) [25]. Supplementary material associated with the models of TB care in this region are available online from https://doi.org/10.6084/m9.figshare.16834648.v1. Across all four models of TB care, the primary mode of diagnosis was via sputum collection. Appropriate specimens for the diagnosis of extrapulmonary TB were rarely collected in these remote Australian border clinics. Mycobacterial culture, phenotypic drug susceptibility testing and genotyping were available throughout the study period and were performed on at least one specimen per patient in the Queensland Mycobacterium Reference Laboratory in Brisbane (Fig 1) [24]. The major differences in care resulting from these changes were reduction in time to treatment commencement and retention in care [26].

Between 2000 and 2012, some treatment for DR-TB was available for PNG nationals diagnosed with DR-TB in Australian border clinics, however, access to treatment was improved between 2006 and 2012 with the establishment of frequent outreach TB clinics in the Torres Strait. The change from the 2000–2005 model of TB care to the 2006–2012 model of TB care was in direct response to Australian Government decisions to invest in TB management of PNG patients from two outer Torres Strait Islands, Boigu and Saibai [27]. The 2013–2015 model of TB care is reflective of Government decisions to stand-down these outer island clinics and increase support and funding for TB health services on the PNG side of the border [28]. As a result, PNG residents diagnosed from 2013 onwards were referred back to the PNG health system for treatment and management. Government decisions to invest in a local Torres Strait-based TB Control Unit with the aim to more rapidly and appropriately respond to presumed TB and confirmed DR-TB cases occurred from 2016, and is ongoing [29]. All Australian residents in this study were managed within the Australian public healthcare system.

Data collection

The Queensland Health's Notifiable Conditions System (NoCS) was used as the source for TB notification data. Only cases with laboratory confirmed DR-TB were included in the study. We used Queensland Health's laboratory software (AUSLAB) as cross-reference. One case was added to the study where their drug-resistant status was identified in AUSLAB, but not registered in NoCS.

Relevant biomarker data (haemoglobin, albumin, lymphocyte levels) were obtained from AUSLAB. Routinely collected biomarker data were analysed, but the fact that it was not consistently available in all patients may have introduced some selection bias.

The management of DR-TB at the Torres Strait / PNG border presents challenges as it involves patients from two countries accessing health systems on both sides of the border in a very remote geographical location. Given the level of interaction between inhabitants, and the increased risk of DR-TB transmission in this cross-border region [9, 10], outcomes for patients

with DR-TB from both sides of the border needed to be considered to evaluate the management of DR-TB in this complex context [30]. Hence, the main strength of this study lies in the linkage and analysis of different data sources. Data from the Queensland Department of Health sources (NoCS and AUSLAB) and the local electronic patient information system used in the Torres Strait called 'Best Practice' were linked to obtain detailed information for each patient included in this study. This data linkage resulted in a more comprehensive insight into the management of DR-TB in the region.

Definitions

In this study, we used WHO definitions [31], where unfavourable treatment outcome was defined as death, lost to follow up or treatment failure. Successful treatment outcome was defined as completed treatment or cured. Transferred out, indicated that the patient was referred back to the PNG health care system. In some patients that were transferred out, treatment outcome was unknown.

Comorbidities were defined as HIV infection, diabetes and renal impairment. Patients with comorbidities recorded as renal dysfunction, renal insufficiency, renal disease and renal failure were all defined as having renal impairment.

With reference to haemoglobin levels, anaemia was defined as those with a Z score at least 2 standard deviations (SD) away from the mean, and severe anaemia was defined as those with a Z score that was at least 5SD away from the mean. This resulted in our definition of anaemia fitting with the laboratory definition of below the reference range, for a given laboratory and patient profile. Within laboratory software AUSLAB, the result is documented in an orange-coloured if it is at least 2SD away from the mean (anaemia) and in a red-colour if at least 5SD away from the mean (severe anaemia) [32]. Similarly, low albumin and lymphocyte levels were defined as those with a Z score at least 2SD away from the mean.

Data analyses

Statistical analyses were performed using IBM SPSS Statistics, version 25 (2019, Armonk, New York, United States). Frequencies and percentages were calculated for descriptive data including age categories, sex, country of birth, visa status, primary health centre (PHC) attended, programmatic diagnosis year group, site of disease, case type, comorbidities, drug resistance, cough and known close contact status. Pearson's Chi-squared tests were carried out to assess whether age group, sex, country of birth, visa status, and PHC attended were associated with unfavourable treatment outcomes.

Potential categorical predictors (site of disease, HIV infection status and comorbidities, case type, drug resistance and selected biomarkers including haemoglobin, lymphocytes and albumin), were analysed by unfavourable, successful or unknown treatment outcome using Fisher's exact or likelihood ratios, except for ethionamide resistance and lymphocyte levels where Pearson Chi-Square was used to ascertain if there was a statistically significant association between these factors and treatment outcomes. Likelihood ratios were used to assess the association between unfavourable treatment outcome and more than one categorical variable. The categorical variable 'diagnostic year group' was included in the analysis as a clinical covariate to account for programmatic changes in the clinical management of TB over time.

In all univariate and multivariate logistic regression analyses, multiple imputation was applied and pooled results from five imputations were used as 19 DR-TB cases did not have any biomarker results available. Biomarker Z scores were imputed for incomplete variables and were further defined as nominal (unfavourable or other) prior to imputation. To overcome differences in reference range parameters that were automatically applied by Queensland

Health's laboratory software, AUSLAB to biomarker results based on sex and age, Z scores were calculated in Microsoft Excel version 2016.

Univariate analysis of comorbidities, diagnosis year group, contact with a known case, biomarkers, acid-fast bacilli (AFB) positivity and rifampicin-resistance were examined as potential predictors of unfavourable outcome using binary logistic regression. All predictor variables were considered for multivariate regression. The regression method was a forward algorithm with entry criteria of $p < 0.05$ from the univariate analyses followed by a backward algorithm with back entry criteria of $p > 0.05$. The level of significance was set at $p < 0.05$ for all analyses.

Ethics

The Far North Queensland Human Research Ethics Committee (HREC) (HREC/17/QCH/74-1157) granted a waiver of consent and use of anonymized data, and approved the study, as did the Chair of James Cook University HREC, (H7380). Further approval was obtained to access case notification data via a Public Health Act application (QCH/36155–1157).

Results

In total, we identified 133 DR-TB patients during the study period. There were 22 deaths and one treatment failure, 16 were lost to follow up and 51 were transferred out. Of the 51 that were transferred out, 41 had no recorded outcome. As shown in Table 1, Boigu Island PHC received fewer patients than Saibai Island PHC but had marginally greater treatment success (49% vs 38%). The median age was 28 years, and patients in the 15–29 years age group were both the largest group and disproportionately affected by unfavourable treatment outcomes. Of six adults aged ≥60 years, 83% ($n = 5$) had an unfavourable treatment outcome. Being a PNG national rather than an Australian Torres Strait Islander was highly predictive of unfavourable treatment outcome.

Table 2 shows that DR-TB patients diagnosed between 2000 and 2005 were more likely to have unfavourable treatment outcomes (50%; $n = 7$) than those diagnosed between 2016 and 2020 (17%; $n = 2$). Overall, outcome improved in recent years with a 50% increase in the chance of a successful outcome between 2016–2020, when compared to all other programmatic year groups; OR 5.3, 95% Confidence Interval (CI) [1.3, 20.4]. Of 133 DR-TB cases, 67% ($n = 89$) had MDR-TB and of those, 74% ($n = 66$) were new cases and 32% had an unfavourable treatment outcome. Ethionamide resistance was only identified in patients diagnosed with MDR-TB ($p < .001$); 90% ($n = 80$) of MDR-TB cases were found to be ethionamide resistant. Nearly one in five patients had previously received full or partial treatment in Australia or PNG. The composite comorbidity variable comprised of nine patients with DR-TB and HIV infection, diabetes and/or renal impairment. Of four patients with DR-TB/HIV coinfection, and three patients with DR-TB/diabetes comorbidity, none had a successful outcome. Overall, 78% ($n = 7$) of patients with DR-TB and at least one comorbidity had an unfavourable treatment outcome.

Table 3 shows that 86% ($n = 92$) of patients with haemoglobin recorded had anaemia, and of those, 38% ($n = 35$) had severe anaemia. Low albumin was detected in 76% ($n = 80$) of patients, where this was measured. A large percentage of patients with low lymphocyte levels, (44%; $n = 43$) had an unfavourable treatment outcome.

In Table 4, patients with comorbidities, low lymphocyte levels and AFB positivity were significantly more likely to have unfavourable treatment outcomes. Being a close contact of a known TB case was a protective factor and reduced the odds of an unfavourable treatment outcome occurring (p .008; OR .31). Although the p value for anaemia in Table 3 was > .1, this

Table 4.4.1 Demographic characteristics and treatment outcome of all patients diagnosed with drug-resistant tuberculosis in the Torres Strait Islands between 2000 and 2020

Demographic characteristic	Treatment Outcome N = 133 (%)[1]							
	Successful		Unfavourable			Transferred Out		p-value
	Cured	Completed	Died	Failed	Lost to follow up		Total	
Age group								**0.02**
<5 years	2 (22)	5 (56)	0 (0)	0 (0)	0 (0)	2 (22)	9	
5–14 years	1 (10)	3 (30)	1 (10)	0 (0)	2 (20)	3 (30)	10	
15–44 years	9 (9)	30 (32)	15 (16)	0 (0)	14 (15)	27 (28)	95	
45–59 years	0 (0)	2 (15)	2 (15)	0 (0)	0 (0)	9 (70)	13	
≥ 60 years	1 (17)	0 (0)	4 (67)	1 (17)	0 (0)	0 (0)	6	
Sex								0.7
Female	9 (12)	22 (30)	14 (19)	1 (1)	8 (11)	21 (28)	75	
Male	4 (7)	18 (31)	8 (14)	0 (0)	8 (14)	20 (35)	58	
Country of Birth								**0.02**
Australia	3 (50)	2 (33)	1 (17)	0 (0)	0 (0)	0 (0)	6	
Papua New Guinea	10 (8)	38 (30)	21 (17)	1 (1)	16 (13)	41 (32)	'127	
Visa Status								**0.002**
Australian resident	3 (33)	3 (33)	2 (22)	1 (11)	0 (0)	0 (0)	9	
Papua New Guinea Treaty Visitor	5 (6)	23 (27)	15 (17)	0 (0)	13 (15)	30 (35)	86	
Papua New Guinea non-Treaty Visitor	5 (13)	14 (37)	5 (13)	0 (0)	3 (8)	11 (29)	38	
Primary Health Centre Attended								1.0
Saibai Island	11 (10)	32 (29)	19 (17)	1 (1)	14 (13)	33 (30)	110	
Boigu Island	2 (13)	7 (44)	2 (13)	0 (0)	2 (13)	3 (19)	16	
Murray Island	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)	2	
Darnley Island	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	1 (50)	2	
Yorke Island	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	1 (50)	2	
Thursday Island	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	1	

[1] Percentages may not equal 100 due to rounding.

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variable was included in the univariate analysis as other studies have demonstrated an association between anaemia and unfavourable treatment outcomes [33], however in this study, anaemia was not a significant predictor of unfavourable treatment outcomes. In the adjusted multivariate model, comorbidities, being a close contact of a known TB case and low lymphocyte levels retained significance ($p < 0.05$).

Discussion

Few reports focus on the specific challenges and unique health care access issues experienced by DR-TB patients in remote settings like the Torres Strait / PNG border region. This study identified variables associated with unfavourable treatment outcomes in patients diagnosed with DR-TB and examined the impact of four different models of TB care over two decades. We documented a significant improvement in successful treatment outcomes once a local decentralised TB control unit was established in 2016. Patients diagnosed before 2013 had the worst treatment outcomes, which is reflective of a time when accessibility to mycobacterial culture and drug susceptibility testing was not routinely available on Daru Island in PNG, and where access to second-line TB drugs was only available for Western Province PNG nationals

Table 4.4.2 Clinical variables of patients diagnosed with drug-resistant tuberculosis in the Torres Strait between 2000 and 2020, and their association with good, unfavourable and other TB treatment outcome

Variable	Treatment Outcome				
	N = 133 (% of total)				
	Unfavourable	Successful	Transferred out	Total	p-value
	(N = 39; 29%)	(N = 53; 40%)	(N = 41; 31%)		
Diagnosis Year Group*^				133	**0.045**
2000–2005	7 (50)	5 (36)	2 (14)	14	
2006–2012	26 (27)	37 (39)	33 (34)	96	
2013–2015	4 (36)	2 (18)	5 (46)	11	
2016–2020	2 (17)	9 (75)	1 (8)	12	
Disease Site				133	0.08
Pulmonary TB	25 (34)	22 (30)	26 (36)	73	
Extrapulmonary TB	2 (20)	7 (50)	1 (10)	10	
Both PTB and EPTB	12 (24)	24 (48)	14 (28)	50	
Cavitary Disease	16 (42)	12 (32)	10 (26)	38	0.1
Case Type				133	0.2
New	29 (27)	41 (38)	37 (35)	107	
Full or partial treatment overseas	8 (38)	11 (52)	2 (10)	21	
Full or partial treatment in Australia	2 (40)	1 (20)	2 (40)	5	
Comorbidities				133	**0.003**
Diabetes Mellitus, Renal Disease or HIV infection	7 (78)	0	2 (22)	9	
No known risk factors	32 (26)	53 (43)	39 (32)	124	
Drug Resistance				133	**0.04**
Isoniazid (mono)	5 (14)	16 (46)	14 (40)	35	
Rifampicin (mono)	3 (75)	1 (25)	0	4	
MDR-TB	29 (33)	33 (37)	27 (30)	89	
Other (streptomycin mono)	2 (40)	3 (60)	0	5	
Ethionamide				133	0.8
Ethionamide resistant	24 (30)	30 (38)	26 (33)	80	
Susceptible	15 (28)	23 (43)	15 (28)	53	
Cough				114	0.1
Cough	27 (31)	31 (36)	29 (33)	87	
No cough	4 (15)	15 (56)	8 (30)	27	
Close Contact#				133	**0.02**
Close contact	8 (16)	23 (45)	20 (39)	51	
No known contact	31 (38)	30 (37)	21 (26)	82	

Note. Unfavourable treatment outcome—died, failed, lost to follow up; successful outcome—cured, completed treatment; other—transferred out

*Diagnosis year group was included as a variable due to changes in the clinical management of DR-TB patients over time.

^OR 5.3, 95% CI [1.3, 20.4], where diagnostic year group 2016–2020 versus all other year groups was analysed as a categorical variable by successful treatment outcome versus unfavourable treatment outcome or transferred out

#Close contact to a known TB case as reported by patient.

PTB, pulmonary TB; EPTB, extrapulmonary TB; MDR-TB, multidrug-resistant TB.

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via Australian TB clinics [34]. For patients diagnosed between 2013 and 2015 in this study, a higher proportion had an unknown outcome. This is consistent with the changeover from the 2006 to 2012 TB management model of increased surveillance and detection at border clinics, to a handover period whereby PNG patients diagnosed at Australian border health facilities were referred back to the PNG health system for ongoing management and care.

Table 4.4.3 Blood test abnormalities in patients diagnosed with drug-resistant tuberculosis in the Torres Strait between 2000 and 2020, and their association with treatment outcome

Variable	Treatment Outcome n (%)			
	Unfavourable	Other	Total	p-value
Haemoglobin Levels* (50-146L)			107	0.5
No anaemia	3 (20)	12 (80)	15	
Mild anaemia	20 (35)	37 (65)	57	
Severe anaemia	10 (29)	25 (71)	35	
Lymphocyte count# (0.04–9.80L)			106	**0.01**
Normal	13 (21)	50 (79)	63	
Low	19 (44)	24 (56)	43	
Albumin# (<15–48L)			105	0.07
Other (normal or high)	4 (16)	21 (84)	25	
Low	28 (35)	52 (65)	80	

*Mild anaemia, at least 2 standard deviations (SD) away from the mean; severe anaemia, at least 5SD away from the mean; #Low lymphocyte and albumin, at least 2SD away from the mean.

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From 2016 onwards, TB clinicians were based in the Torres Strait and therefore able to rapidly respond to cases diagnosed, associated contact tracing efforts and monitoring of treatment compliance and outcomes for patients. Higher success rates for DR-TB patients have been reported in countries where patients have access to developed health infrastructure and where skilled clinicians are positioned to support DR-TB patients [35]. From 2016, local nurses and Indigenous Health Workers undertook Directly Observed Therapy for TB patients residing in the Torres Strait. Collegial relationships between TB programs in the Torres Strait and Daru Island were also strengthened through this period with the joint development of procedural documents and processes [36] which enabled each TB program to define data requirements, streamline the exchange of shared patient information, and enhance surveillance capability. These strengthened relationships may help to explain the reduction in unknown treatment outcomes in this study from 2016. These initiatives are consistent with the Australian National Tuberculosis Advisory Committee (NTAC) recommendations to engage in regional and bilateral collaborations in order to improve TB services in cross-border areas [37].

It is widely accepted that household contacts of DR-TB patients are at greater risk of exposure, infection and disease progression when compared with other types of contacts [38]. In a

Table 4.4.4 Variables associated with unfavourable treatment outcome among drug-resistant tuberculosis cases diagnosed in the Torres Strait/Papua New Guinea border region between 2000 and 2020 (N = 133)

Variable		Unfavourable outcome	Univariate Analysis		Multivariate Analysis	
	n (%)	n (%)	OR (95% CI)	p-value	aOR (95% CI)	p-value
Comorbidities (DM, renal, HIV infection)	9 (7)	7 (78)	10.06 (1.98–50.96)	**0.005**	17.4 (2.6–117.06)	**0.003**
Contact with known TB case	51 (38)	8 (16)	.3 (.12-.73)	**0.008**	.3 (.08-.87)	**0.03**
Low lymphocyte level	43 (32)	19 (44)	3.05 (1.29–7.17)	**0.01**	2.7 (1.1–7.08)	**0.04**
AFB positive	80 (60)	29 (36)	2.4 (1.07–5.58)	**0.03**	1.6 (.56–4.48)	0.4
Rifampicin resistance	93 (70)	32 (34)	2.5 (.96–6.21)	0.05	Eliminated at forward step	
Anaemia	93 (70)	30 (32)	1.9 (.50–7.26)	0.3	Eliminated at forward step	
Low albumin level	80 (60)	28 (35)	2.8 (.88–9.05)	0.08	Eliminated at forward step	
Female sex	75 (56)	23 (31)	1.2 (.55–2.47)	0.7	Eliminated at forward step	

Note. aOR, adjusted odds ratio; CI, confidence interval; DM, diabetes mellitus; renal, renal impairment; HIV, human immunodeficiency virus; AFB, acid-fast bacilli.

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study of MDR-TB index cases in Pakistan, MDR-TB diagnoses were reported in 17.4% of close contacts [38]. Unlike isoniazid-resistant TB which is more amenable to treatment, patients with MDR-TB may be more likely to remain infectious longer than patients with drug susceptible TB [39], thus increasing the likelihood of transmission to close contacts. Despite the increased transmission risk, close contacts had more favourable outcomes in this study. A possible explanation is that these close contact patients were actively screened, or linked in with healthcare services earlier because of raised awareness, leading to earlier diagnosis and potentially improved treatment adherence. Better outcomes for close contacts after 2014 may also be attributed to improved health literacy and symptom recognition as a result of mass community education offered in the region from 2014 [40].

This retrospective study has a number of limitations. Details of the drug regimens used for individual patients in this study were not available for analysis, however twice and thrice weekly dosing of second-line drugs was available for some MDR-TB patients treated between 2006 and 2015. From 2016, clofazimine and linezolid were included in most MDR-TB regimens in the region per WHO recommendations [41], and bedaquiline was first used in the region in 2018. The study did not identify the type of close contact (i.e. household contact), nor ascertain the type of TB that each close contact was exposed to. The recent upgrade of the Mabadauan health centre in PNG will aid the PNG health system's capacity to manage close contacts in border communities. It will, however, be important that expanded diagnostic capabilities at Mabadauan, are matched with capacity to retain patients in the TB care pathway [35]. Since 2016, the Torres and Cape TB Control Unit has collected and shared TB contact tracing data with Daru General Hospital, related to all PNG residents diagnosed with TB in the Torres Strait. It is anticipated that increased capacity of local health services available to residents of PNG living adjacent to the Torres Strait, may lead to effective TB contact management, further improve treatment outcomes for PNG patients diagnosed with DR-TB as well as support TB patients with other comorbidities.

Patients with pre-existing comorbidities in this study were significantly more likely to have unfavourable treatment outcomes, which is consistent with earlier findings [6, 42, 43]. In our study, no patients with a serious comorbidity were cured or completed treatment. HIV is a major risk factor for TB disease development and associated with unfavourable treatment outcome in the absence of successful HIV care, which is a major concern in the study setting. However, HIV is unlikely to be a major contributing factor in community TB transmission dynamics as currently less than 1% of the population is HIV infected [44]. It is possible that 'stand-alone' vertical disease programs for TB control, diabetes management and sexual health, may contribute to poor linkage of care and unfavourable treatment outcomes for DR-TB patients with a comorbidity [45]. It would be beneficial for TB programs to establish strong linkages with both diabetes educators and sexual health providers to provide enhanced screening, monitoring and management support for patients with these comorbidities [46]. As there were no protocols in places to consistently screen TB patients for diabetes or renal impairment during this study period, it is possible that comorbidities have been under-reported in this study.

In renal patients, delayed TB diagnosis is a possible reason for unfavourable outcome [47]. Aboriginal and Torres Strait Islander peoples develop chronic kidney disease three times as often as non-Indigenous Australians [48] and in Torres Strait Islander adults, a recent survey found that nearly one in five people showed signs and symptoms of chronic kidney disease [49]. Renal impairment is more likely to be documented in residents of the Torres Strait Islands due to their relative ease of access to ongoing health services in the region. By contrast, an absence of renal dialysis in the Treaty villages suggests there would be limited survival of PNG patients with kidney disease. As uremic symptoms like fever and weight loss are non-

specific symptoms of both TB and renal disease, renal physicians would be well placed to consider TB as a differential diagnosis and monitor patients with insidious onset of these symptoms [47]. Early detection of TB in renal patients may be key to improved outcomes [47]. Efforts to increase collaboration between renal and TB units in the Torres Strait may help reduce diagnostic delay and better support shared patients. Many studies have reported high rates of mortality in TB patients with comorbidities [47, 50–52] and in patients with low levels of haemoglobin, albumin and lymphocytes [53].

Although not consistently measured, low lymphocyte levels were statistically significantly associated with unfavourable treatment outcomes in DR-TB patients, and also among HIV uninfected patients, which is consistent with findings in other studies [54]. In patients who were previously lost to follow up or with past treatment failure, overall health decline evidenced by low lymphocyte levels can be a marker for disease severity and complexity [55]. When compared to drug susceptible TB, lower lymphocyte counts have been reported in MDR-TB patients [56]. Low lymphocyte counts, as well as haemoglobin and albumin levels, are all indicative of general poor health at the time of treatment initiation.

Low haemoglobin and albumin levels have been identified as strong predictors of TB mortality [57] and in China and Israel, an association between hypoalbuminaemia and poor prognosis in DR-TB patients has been reported [7, 58]. A study conducted in Ethiopia reported that MDR-TB patients with low haemoglobin levels (anaemia) were more than twice as likely to have unfavourable treatment outcomes when compared to patients without anaemia [42]. Low haemoglobin has also been associated with unfavourable treatment outcomes in non-MDR TB patients, specifically with delayed sputum conversion at two months [59]. It is possible that the anaemia observed in DR-TB patients is due to nutritional iron deficiency and not chronic disease [33], however this study did not explore levels of iron, ferritin, hepcidin and transferrin in TB patients or assess haemoglobin levels in the general population.

Several limitations have already been described above. Another limitation of this study is that only people with laboratory-confirmed DR-TB isolates were included, excluding those with drug susceptible TB or unconfirmed DR-TB. This therefore represents a very select group and limits our ability to comment on general trends and outcomes. We were however able to compare those with and without rifampicin resistance, finding a trend to worse outcome in those with rifampicin resistance.

Apart from selection bias, the relatively small number of patients also affected the power of our statistical analyses. Future studies could incorporate drug-susceptible patients as well, which would provide a more generalizable comparator. We were unable to ascertain whether the cause of death for all patients was TB, however, patient death was documented during the time period for the course of TB treatment for all patients. As this was an observational study of care delivered over time, we acknowledge that there may be confounding factors, linked to changes in clinical care and the availability of new diagnostic tools and treatment options.

Conclusion

Although having a locally-based TB program in the Torres Strait has resulted in better treatment outcomes for DR-TB patients, more interventions to improve treatment outcomes and refine the focus on vulnerable sub-populations are needed. Most patients with comorbidities in this study had an unfavourable treatment outcome and poor health indicators suggesting late presentation or underlying poor management of their comorbidity. These findings have important implications for TB programs on both sides of this international border. Key strategies should include strong cross-border working relationships, as well as better collaboration with diabetes, renal and sexual health care providers to identify and manage TB in patients.

There should be an ongoing commitment to enhance HIV care and to improve the care of DR-TB patients at-risk of unfavourable treatment outcomes.

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Figure 5.1 Thursday Island Hospital campus (Foster, 2016)

Chapter 5: High Price

The main resistance is always about cost and always relates to the poor

- Dr Paul Farmer, Founder of Partners in Health –
in Documentary: "Bending the Arc", 2017.

Overarching Aim #2: Identify opportunities for evidence-based enhanced policy and practice for the management of TB in the region (Translational Research).

Overarching Aim #3: Identify opportunities for strengthened cross-border communication and collaboration between Australia and PNG health services to better manage TB in the region.

Overarching Aim #4: Assess the aeromedical evacuation efficiency for TB in the Torres Strait and evaluate decision-making for PNG nationals with presumptive TB at the Australia / PNG border.

Aims:

1. Identify the cost of aeromedical retrieval and medical management of an exemplary TB patient from PNG into the Australian health care system.
2. Determine the median length of stay in the Australian health care system for PNG Nationals who have been diagnosed with TB and medically evacuated from the TSPZ.
3. Explore adherence to Policy in relation to clinical deterioration detection scores.
4. Assess the impact of clinical deterioration detection score and their useability in patients presenting with signs and symptoms of TB in an endemic setting.

5.1 Cost of tuberculosis-related aeromedical retrievals in the Torres Strait: A Case Study

5.1.1 Aims

1. Identify the cost of aeromedical retrieval and medical management of an exemplary TB patient from PNG into the Australian health care system.

2. Determine the median length of stay in the Australian health care system for PNG Nationals who have been diagnosed with TB and medically evacuated from the TSPZ.

In this descriptive paper, I outline the funding model used to provide health care for residents of PNG that present to health facilities in the Torres Strait Protected Zone. I provide a complete and complex breakdown of costs incurred to medically evacuate and manage one exemplary PNG national diagnosed with TB that required advanced healthcare within the Australian hospital system. I use information collected from Queensland Health, Queensland Ambulance Service and the Aeromedical Retrieval and Disaster Management Branch. I also identify the number of PNG patients diagnosed with TB between 2016 and 2019 who were medically evacuated to an Australian hospital, including the median length of hospital stay. For this component, I use data sourced from the Notifiable Conditions System. Outputs of the assessments are 1) total funds provided over four years are insufficient to cover costs incurred to medically evacuate and manage patients in critical conditions seeking healthcare via the Torres Strait Protected Zone; and 2) the median length of stay for PNG national patients entering the Australian hospital system via the Torres Strait Protected Zone is greater when hospitalisation in both Thursday Island and Cairns Hospitals is required.

5.1.2 Publication Contribution

I was the lead author of the following manuscript (pending peer-review publication). My contribution to the study and subsequent outputs were as follows:

- I developed the concept for this study.
- I contributed to the design of this study.
- I wrote the ethics and site-specific authorisation applications and obtained clearance to use data for this paper.
- I wrote the Public Health Act authorisation application and obtained clearance to access data for this paper.
- I collected the data for this study.
- I used Excel and SPSS to organise the data collected and attended to all coding.
- I conducted the analysis with results reviewed by my supervisory team.
- I was the lead author of the manuscript which I initially drafted.
- I shared draft versions of this manuscript with stakeholders for review for accuracy of detail.

- I managed the submission of this manuscript which was peer-reviewed and accepted for publication.
- I prepared various presentations that included the results from this study for the Torres and Cape Hospital and Health Service Board – Safety & Quality Committee (29.04.21); Queensland Health Directors of Clinical Governance Implementation and Improvement Partnership (11.06.21) and the National Tuberculosis Advisory Committee (22.06.21).

5.1.3 Translation Research

- I discussed the findings of the study with the Honourable Warren Entsch, Federal Member for Leichhardt, Far North Queensland, to create an awareness of the shortfall in Federally allocated funding.
- I shared the findings of this study with the Queensland Health Department of Strategy who are responsible for submitting applications for Federal Government funding for Torres Strait / PNG cross border funding every four years.

Cost of tuberculosis-related aeromedical retrievals in the Torres Strait, Australia

J'Belle Foster, Daniel Judge, Diana Mendez, Ben Marais, Dunstan Peniyamina, Emma McBryde

ABSTRACT

Objectives: Tuberculosis (TB) remains a disease of public health significance at the Australia / Papua New Guinea (PNG) international border. In the remote Torres Strait Islands of Queensland, Australia, aeromedical evacuation is a necessary but costly component of TB management and patients with critical care needs require support to prevent onward TB transmission.

Methods: A detailed costing of an exemplar TB patient from PNG who presented to a Primary Health facility in the Torres Strait and required urgent aeromedical evacuation was performed. Data were drawn from patient charts, and financial and clinical information systems used within Queensland Health and the Torres and Cape Hospital and Health Service.

Results: The total cost of aeromedical evacuation was $124,280 in Australian dollars; 54% of the cost was attributed to travel. Between 2016 and 2019, 19 patients diagnosed with TB were medically evacuated from an outer Torres Strait Island with a median length of hospital stay of 57 days.

Conclusion: Aeromedical evacuation and medical management costs require adequate budget allocation.

Acknowledgments: This work was supported by the Torres and Cape Hospital and Health Service Revenue Manager located on Thursday Island. The authors are grateful to the Queensland Aeromedical Retrieval and Disaster Management Branch and the Queensland Ambulance Service for access to data and revision of relevant sections within the manuscript.

Introduction

The Papua New Guinea (PNG) / Torres Strait border area is potentially a major source of drug susceptible, mono-resistant, drug-resistant and multi-drug resistant TB (MDR-TB) into Australia.[1] At the closest point, the Torres Strait Islands in Queensland are less than 5kms from PNG's Western Province.[2] Cross border dynamics and current TB prevention and control

efforts are largely attributable to geographical, regional, political and administrative complexities and structures.[3] Prior to international border closures in March 2020 due to the COVID-19 pandemic,[4] the Torres Strait Treaty allowed residents of 13 Treaty villages in the Western Province of PNG and 14 communities of the Torres Strait Islands in Australia to cross the international border for traditional purposes without health checks, visas or passports[5] (Figure 5.1.1). This freedom of movement coupled with the conservative TB incidence rate of 674 cases per 100,000 population in the Western Province of PNG,[6] places the Indigenous population of the Torres Strait Islands of Queensland, Australia particularly vulnerable to TB transmission.[7]

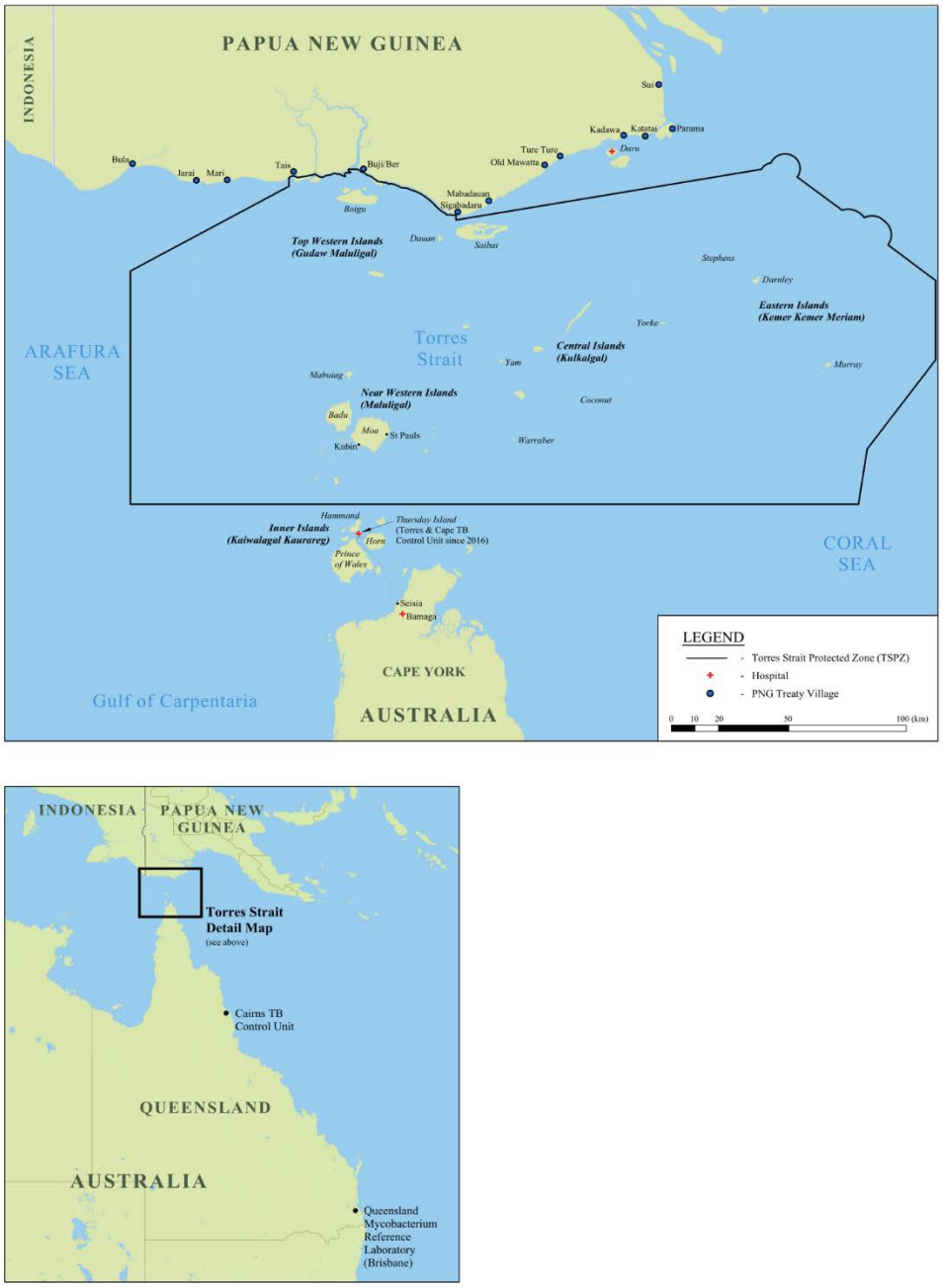

Figure 5.1.1 Map of A) the Torres Strait / Papua New Guinea border and Torres Strait Protected Zone and B) Greater Queensland with relevant TB referral centres. CC BY 4.0[1]

[1] Traditional inhabitants of the Torres Strait Protected Zone and Treaty villages may cross this international border without passport or visa. DOI. 10.6084/m9.figshare.16632823

PNG Treaty villages are among the poorest and most remote in PNG and lack access to clean running water and electricity.[2] Health service provision in the PNG Treaty villages is poor and

in 2018, seven basic medical units and one health centre were frequently unstaffed or unstocked with basic medical supplies. The closest major health facility from the Treaty villages in the Western Province of PNG, is Daru General Hospital, located at least two hours away by personal boats powered by small outboard motors.[2] Hence, PNG residents frequently cross the narrow stretch of water separating the two countries to attend well-resourced Queensland Health Primary Health facilities located in the Torres Strait Islands in Australia.[3]

Aeromedical evacuation is a necessary component of Queensland Health's obligation to provide critical health care services to anyone presenting to Torres and Cape Hospital and Health Service (TCHHS) primary health centres (PHCs) in the Torres Strait Protected Zone (TSPZ) including residents of PNG that live adjacent to the Torres Strait Islands (Figure 5.1.1). In recognition of health services provided to PNG nationals within the Queensland Health system, funding provided through the Commonwealth's 'Managing Torres Strait / Papua New Guinea Cross Border Health Issues (Schedule B) National Partnership Agreement', was $18.9 million in Australian dollars (AUD), between 1 July 2016 to 30 June 2020, averaging AUD 4.7 million per year.[8] This study describes detailed costing of the medical evacuation and medical management of one PNG national patient diagnosed with pulmonary TB who presented to Boigu Island in 2019 and who was subsequently admitted to both Thursday Island and Cairns Hospitals (Figure 5.1.1).

Medicare is Australia's health insurance scheme which provides free or low-cost access for all Australians to public hospitals, other medical services and medication.[9] Typically, overseas visitors whose countries do not have a Reciprocal Health Care Agreement with Australia are considered to be Medicare ineligible.[10] Medicare ineligible patients are responsible for fees and charges associated with both outpatient and inpatient care in Queensland.[10] As PNG does not have a Reciprocal Health Care Agreement with Australia,[11] PNG nationals without a Medicare card who enter Australia via a designated port, must pay for health services received. The exception to this rule is for PNG nationals who enter the Australian health care system via the TSPZ.[12] While these patients are still Medicare ineligible, costs incurred for managing and treating them are absorbed by Queensland Health Hospital and Health Services (HHSs), with partial funding to offset costs provided by the Australian Government Department of Health. This, in addition to remoteness and travel, are some of the reasons that the cost of health care per capita / per service rendered, is higher for HHSs in Far North Queensland than is typical across funding structures in other HHSs in Queensland.[12]

The Australian Government provides important and strategic funding to manage the delivery of health services to PNG nationals which specifically includes but is not limited to the management of TB patients[8] to address transmission risk from PNG to Australia.[13] This funding is not intended to be used for PNG patients who have arrived in Australia with a passport at an authorised port, rather, it is designated for HHSs to provide healthcare to PNG nationals entering via the TSPZ. At no 'out of pocket' expense for PNG patients, funding includes but is not limited to: hospital admissions, outpatient services, management of TB patients, pathology, pharmaceuticals and patient transport.[8] Although Schedule B of the National Partnership Agreement states that funding for health services rendered includes '*patient transport (such as medical evacuations)*',[8] the Commonwealth funding does not cover the majority of expenses incurred by the services undertaking or supporting aeromedical evacuations such as Aeromedical Retrieval and Disaster Management Branch (ARDMB)-supported aeromedical evacuation, and these additional costs are borne by Queensland Health. This Federal funding allocated to managing PNG nationals seeking health care via the TSPZ is absorbed into the total funding pool for all health services rendered in HHSs.

Materials and Methods

The journey of a PNG national patient who presented to Boigu Island PHC in a critical condition and diagnosed with fully-susceptible pulmonary TB, was selected to cost a typical aeromedical retrieval case of TB. The case was considered typical (without excessive additional costs) as the patient was not accompanied by an escort and did not have drug-resistant TB or comorbidities which may have resulted in an extended hospital admission.

A micro-costing 'ingredients' economic evaluation approach was undertaken. The cost of services considers fixed costs such as equipment lifespan – cost of medical evacuation. Details of the clinical presentation and pharmaceuticals, pathology, imaging and procedures ordered were reviewed in the TCHHS electronic medical record system, Best Practice, and in the TB patient information database used by the Torres and Cape TB Control Unit. Pathology and imaging services provided were cross checked against Queensland Health's laboratory results database AUSLAB, imaging databases Enterprise PACS and Merlin Web, and state-wide health service database The Viewer.[14] The Viewer and Best Practice were also accessed to ascertain the length of hospital stay for patients who were medically evacuated.

Aeromedical evacuation (Boigu Island to Thursday Island; Thursday Island to Horn Island and Horn Island to Cairns) costs to support this patient were sourced from the ARDMB. The ARDMB centrally manage funding and contracts with the Queensland Department of Health and Queensland Ambulance Service (QAS). QAS fund associated paramedic support when required during aeromedical evacuations in TCHHS. Both ARDMB and QAS sit within Queensland Health.

Clinicians within TCHHS will contact Retrieval Services Queensland (RSQ) with requests for aeromedical retrieval. RSQ are part of the ARDMB and centrally coordinate triaging, and the dispatch of paramedic support and aircraft including the rescue helicopter to respond to medical events requiring aeromedical evacuation.[15,16] The Royal Flying Doctors Service (RFDS) provide additional support for inter-facility transfers between Horn Island and Cairns on fixed-wing aircraft. Costs of RFDS interfacility transfer flights are funded by ARDMB through the Queensland Department of Health as part of a state-wide contract to provide aeromedical support to Queensland communities (Table 5.1.1). ARDMB will then recoup a proportion of costs from TCHHS. Costs were assessed in late 2020/early 2021 and were expressed in Australian dollars. See Table 5.1.S1 for extended methodology.

Written consent from the patient was obtained for this study. Ethical approval was granted by the Far North Queensland Human Research Ethics Committee (HREC) (HREC/17/QCH/74-1157), and the Chair of James Cook University HREC, (H7380). Public Health Act authorisation (QCH/36155 – 1157) was also obtained to access patient data. Written approval was separately obtained from the Queensland ARDMB Research Committee, and Queensland Ambulance Service Torres and Cape York Local Ambulance Service Network.

Results

Table 5.1.1 shows that the cost to medically evacuate and medically manage one PNG national with uncomplicated fully-susceptible pulmonary TB from Boigu Island in 2019 was AUD 124,280. The total cost to medically evacuate the patient was AUD 58,029, with the remainder costs attributed to pathology, outpatient assessment, inpatient stay, pharmaceuticals and other travel. The Rescue 700 flight from Boigu Island to Thursday Island and then from Thursday Island to Horn Island Airport comprised the single biggest expense (AUD 48,900), followed by in-patient care in Cairns Hospital (AUD 45,760).

Table 5.1.1 Cost of managing a Papua New Guinea patient with drug-susceptible tuberculosis (TB) requiring aeromedical retrieval from Boigu Island to the Australian health system in 2019

Activity	Funded via Hospital and Health Services (HHSs)				Funded via Queensland Health but external to HHSs		Total
	Boigu Island Primary Health Centre (TCHHS)	Thursday Island Hospital (TCHHS)	Cairns Hospital (CHHHS)	Torres and Cape TB Control Unit (TCHHS)	Queensland Aeromedical Retrieval and Disaster Management Branch (ARDMB)	Queensland Ambulance Service (QAS)	
Single outpatient clinic visit†	1,141			282			1,423
Outpatient pathology	1,095						1,095
Aeromedical retrieval		6,273§			2,457§ 48,900‡	399††	58,029
Inpatient hospital stay¶		8,005	45,760				53,765
Other travel¶¶		8996					8996
Pharmaceuticals	35	202	735				972
TOTAL	**2,271**	**23,476**	**46,495**	**282**	**51,357**	**399**	**124,280**

† Category 2 Emergency
¶ Includes costs associated with meals, wages, cleaning, diagnostic imaging/procedures and pathology.
§ The total cost of the Royal Flying Doctors Service inter-facility transfer flight from Horn Island to Cairns was $8,730 which was funded by ARDMB through Queensland Department of Health. ARDMB recovered a proportion (72%) of the full amount from TCHHS.
‡ Rescue 700 flight from Boigu Island to Thursday Island and Thursday Island to Horn Island Airport
†† Wages of Queensland Ambulance Service paramedic to travel from Thursday Island to Boigu Island return on the Rescue 700 flight
¶¶ Includes road transfers from Cairns Airport to Cairns Hospital and road transfers and commercial flights from Cairns to Boigu Island to repatriate
Costs rounded to the nearest Australian dollar

The median length of stay in the Australian healthcare system for 19 PNG patients diagnosed with TB and medically evacuated between 2016 and 2019 was 57 days (26-107). The length of stay for the patient in the case study was 24 days. Patients who received care in both Thursday Island and Cairns Hospitals experienced a median length of stay of 102 days,

compared to a median stay of 43 days when receiving care in both Thursday Island and Townsville Hospitals.

Discussion

The economic burden of managing and treating TB patients is clear across different populations, and comparison of previously reported costs, with the cost of managing PNG nationals at the Australian border is complex. The cost to medically evacuate and manage a patient with pulmonary TB in this study was AUD 124,280. This is more than ten-fold higher than the average cost of providing full treatment to fully susceptible TB patients in Victoria, Australia, at AUD 11,583.[17] Similarly, meta-analyses of TB treatment costs in the European Union estimated the average total cost to treat a fully susceptible TB patient was EU 10,282 (AUD 17,213.47).[18] It is important to point out that this patient had drug-susceptible TB, which is associated with greatly reduced in-patient care expense compared to patients with highly drug-resistant TB. Most published cost analyses report the total cost of administering a full course of anti-TB treatment, whereas the primary goal for managing a critically unwell PNG national TB patient entering Australia via the TSPZ is to stabilise, diagnose, commence on treatment and refer back to the PNG health system for continuation of their treatment and care.

In total, TB-related presentations make up a small proportion of all patients who receive and are retrieved for care in the Torres Strait. In a typical year, there are just under 100 aeromedical evacuations from Torres Strait outer islands involving PNG nationals, of which around ten are TB-related. The designated funds provided by the Australian Government Department of Health to compensate Queensland Health for healthcare provision to PNG nationals seeking healthcare via the TSPZ under Schedule B is AUD 4.7million per year. If each aeromedical evacuation costs a similar amount to our case study, there is a total shortfall in funding of over AUD 7.5 million per year to medically evacuate and manage PNG nationals. However, the true costs are unknown as analyses such as in this study are not routinely performed. In addition to better compensation for Queensland Health, greater transparency of expenditure and contractual milestone attainment could be achieved if the funds were held separately instead of being absorbed into HHSs.

As a result of the COVID-19 pandemic-related border closure between Australia and PNG in March 2020, residents of the Treaty villages living adjacent to the Australian border have experienced a reduction in access to TB diagnostics, treatment and critical care, and it is likely

that household transmission of TB has increased during this time. As Australia prepares to open up to the world once more, it will be imperative that Queensland Health are prepared for a potential influx of patients with critical care needs from PNG.

Conclusion

Funding of emergency evacuations for TB and other illnesses in this remote region, is necessary, unavoidable and expensive, and current levels of funding do not meet the demand. The high cost of patient care in such a remote setting, points to the benefit of supporting patients with critical care needs to prevent onward transmission of TB, as well as adequate budget allocation for aeromedical evacuation when required.

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Some Queensland Health and other Government agency documents may not be accessible to the general public.

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Table 5.1.S1. Extended methodology: the cost to medically evacuate and manage one Papua New Guinea national diagnosed with pulmonary tuberculosis within the Australian health system.

The cost of this patient's outpatient and inpatient clinic visits was obtained from Queensland Health's fees and charges register.[19]. Hospital and Health System cost categories included outpatient services confirmed as a Category 2 Emergency, pharmaceuticals, inpatient hospital stay, Royal Flying Doctors Service inter-facility transfer flight and other travel. The cost of inpatient hospital admission for Medicare ineligible patients includes clinician wages, meals, cleaning, pathology / procedures and diagnostic imaging.

Outpatient service expenses provided at Boigu Island Primary Health Centre include wages, cleaning, diagnostic imaging/procedures and pathology. Pharmaceuticals were calculated separately. Wages for the Torres and Cape Tuberculosis Control Unit staff involved in providing an outpatient service to manage this patient were also calculated and reported separately.

Most travel-related costs (excluding aeromedical retrieval within the Torres Strait Islands) are borne by the Hospital and Health System in the jurisdiction where the patient first presented, regardless if additional travel across Queensland was required. All costs were reported separately for each health facility and the total cost of each category was provided.

The costs of pharmaceuticals were calculated by determining the full cost for any one item (i.e. box of Isoniazid 300mgs tablets), and multiplying this cost by the number of boxes or fractions of boxes required (this was obtained by dividing the number of doses administered to the patient by the total number of doses per box). Pathology was calculated per pathology request form rather than per test ordered, as per State billing requirements.[20] Item numbers for imaging services provided were obtained from the Queensland Health Medicare Benefits Schedule (MBS) Radiology Billing Manual[21] and then cross matched for cost from the MBS online.[22]

Travel costs (excluding Boigu Island to Thursday Island; Thursday Island to Horn Island and Horn Island to Cairns) were sourced from the Torres and Cape Hospital and Health System patient travel and finance/revenue teams. These travel costs pertain to commercial flights and patient transport to and from relevant airports and hospitals. Travel costs did not include any expenses incurred by the patient or the Western Provincial Health Authority in Papua New Guinea.

Figure 5.2 Overcrowded boat heading back to Papua New Guinea from Saibai Island (Foster, 2018).

5.2 Critical consideration of tuberculosis management of Papua New Guinea nationals and cross-border issues in the remote Torres Strait Islands, Australia

5.2.1 Aims

4. Explore adherence to Policy in relation to clinical deterioration detection scores.
5. Assess the impact of clinical deterioration detection score and their useability in patients presenting with signs and symptoms of TB in an endemic setting.

In this paper, I determine the deterioration detection scores of all PNG national patients that presented with presumptive TB to health facilities in the Torres Strait Protected Zone between 2016 and 2019. I conduct critical evaluation of patient outcomes and associated clinical decisions as they relate to local policy (Figure 5.2.1). I use information collected from the Torres and Cape TB Control Unit PNG spreadsheet, Best Practice and patient charts. Outputs of the analyses are that 1) implementation of local policy does not guarantee adherence; 2) current scoring systems may not identify the most serious of case presentations; 3) of the patients that met criteria for aeromedical evacuation but were sent back to the PNG health system, more than two thirds died or were lost to follow-up and 4) limitations on the freedom of movement of PNG national patients are being applied that may contravene human rights.

5.2.2 Publication Contribution

I was the lead author of the following peer-reviewed paper. My contribution to the study and subsequent outputs were as follows:

- I developed the concept for this study.
- I contributed to the design of this study.
- I wrote the ethics and site-specific authorisation applications and obtained clearance to use data for this paper.
- I wrote the Public Health Act authorisation application and obtained clearance to access data for this paper.
- I collected the data for this study.
- I used SPSS to generate descriptive statistics.
- I conducted the descriptive analysis with results reviewed by my supervisory team.
- I was the lead author of the manuscript which I initially drafted.

- I managed the submission of this manuscript which was peer-reviewed and accepted for publication.
- I prepared a presentation that included the results from this study for the National Tuberculosis Advisory Committee (22.06.21).
- I shared draft manuscripts with the Chief Executive of the Torres and Cape Hospital and Health Service, and obtained clearance to publish.
- I shared the final draft manuscript with the Queensland Health Communicable Diseases Branch, and obtained clearance to publish.
- "In order to ensure the confidentiality of sensitive information relating to individuals within this publication, information permitting re-identification has been subsequently destroyed, and re-identification or independent validation of individuals within this dataset is therefore no longer possible" (personal communication, co-author JD, 25.09.24).

5.2.3 Translation Research

- I shared the findings of this study with the Torres and Cape Hospital and Health Service Executive Director Medical Services and Director Patient, Safety and Quality, to flag non-adherence to local policy.
- Recognising the potential harm that may come to paediatric PNG patients presenting to Australian health facilities with presumptive TB without a focused sub-speciality deterioration scoring system, chapter 6 of this PhD was borne (Paediatric TB). It is my intention to use evidence derived from chapters 5 and 6 of this PhD to design and implement a TB Scoring system for use in the region.

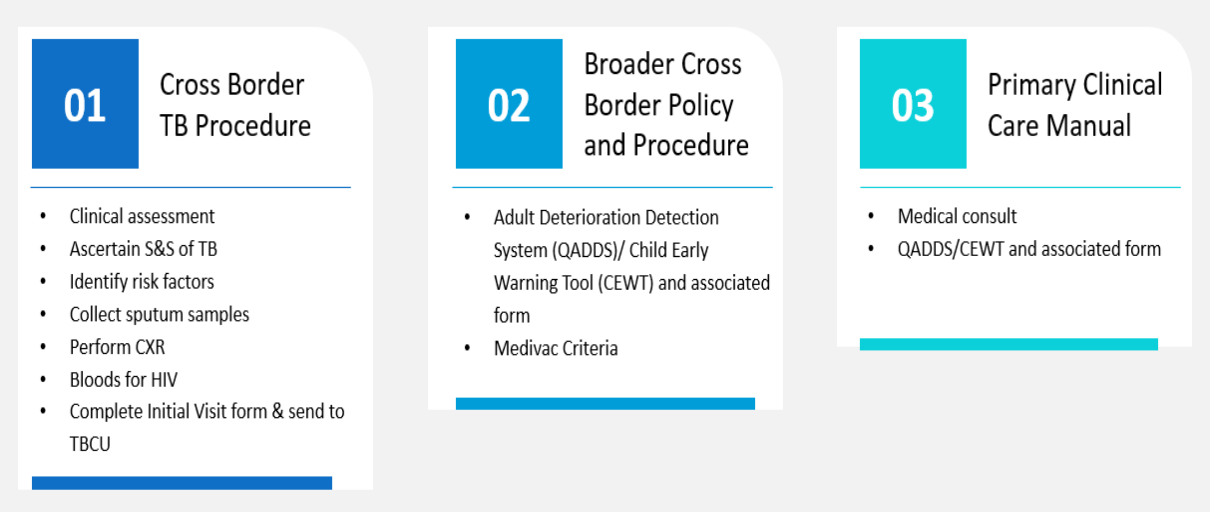

Figure 5.2.1 Existing health policy and procedures used to manage patients with presumptive tuberculosis in the Torres Strait

Results from this study are included in the following peer-reviewed publication.

Tropical Medicine and Infectious Disease

MDPI

Article

Critical Consideration of Tuberculosis Management of Papua New Guinea Nationals and Cross-Border Health Issues in the Remote Torres Strait Islands, Australia

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Abstract: The international border between Australia and Papua New Guinea (PNG) serves as a gateway for the delivery of primary and tertiary healthcare for PNG patients presenting to Australian health facilities with presumptive tuberculosis (TB). An audit of all PNG nationals with presumptive TB who presented to clinics in the Torres Strait between 2016 and 2019 was conducted to evaluate outcomes for PNG patients and to consider the consistency and equity of decision-making regarding aeromedical evacuation. We also reviewed the current aeromedical retrieval policy and the outcomes of patients referred back to Daru General Hospital in PNG. During the study period, 213 PNG nationals presented with presumptive TB to primary health centres (PHC) in the Torres Strait. In total, 44 (21%) patients were medically evacuated to Australian hospitals; 26 met the evacuation criteria of whom 3 died, and 18 did not meet the criteria of whom 1 died. A further 22 patients who met the medical evacuation criteria into Australia were referred to Daru General Hospital of whom 2 died and 10 were lost to follow-up. The cross-border movement of people from PNG into Australia is associated with an emergent duty of care. Ongoing monitoring and evaluation of patient outcomes are necessary for transparency and justice.

Keywords: tuberculosis; Torres Strait; medical evacuation; cross-border

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1. Introduction

High tuberculosis (TB) rates in the Western Province of Papua New Guinea (PNG) (674/100,000 population in 2016) [1] and poor access to health services in the remote villages lead to many residents accessing health services at the Australia/PNG international border [2]. On Daru Island in the Western Province of PNG, an ongoing multidrug-resistant (MDR)-TB outbreak has been reported [3,4]. Cross-border movement of PNG residents of the Treaty villages places residents of the Torres Strait Islands, Australia at risk for TB and MDR-TB transmission [4,5], and options for critical healthcare needs are limited for PNG nationals living adjacent to the Australian border under current bilateral agreements [2,6].

Healthcare is available for residents of both Australia and PNG at primary health centres (PHC) located in the Torres Strait Islands, on the Australian side of the border. Furthermore, patients that present in a critical condition may be medically evacuated to an Australian hospital to receive advanced care [7]. In practice, health care delivery on the Australian side of the international border is supported by medical resources and access

for Australian residents to health care services, medical interventions and follow-up [8]. The Australian Government has invested heavily in the TB control programme in the Western Province, particularly the South Fly region, however, health care provision remains inequitable in this region and location of residence has important implications for health outcomes [9].

1.1. Torres Strait/PNG Context

The Torres Strait Treaty is an agreement between the governments of both Australia and PNG, which was ratified in 1985 [10,11]. The Treaty provides protection for the local inhabitants and their traditional activities on both sides of the border and contains specifications for maritime jurisdiction, fisheries resources, and navigation [10]. Traditional inhabitants of 13 Australian Torres Strait Islands and 13 PNG Treaty villages enjoy cross-border movement without the need for a passport or visa, provided the intended travel is for traditional purposes [11]. The area that encompasses the Australian communities involved in the Torres Strait Treaty is known as the Torres Strait Protected Zone (TSPZ) (see map of Torres Strait/PNG border region at https://doi.org/10.6084/m9.figshare.16632823.v1, accessed on 14 January 2022; authored by J'Belle Foster, Marty Moran, Diana Mendez).

Health care is not considered a traditional activity, and as a result access to Australian health facilities for PNG nationals is not a provision under the Torres Strait Treaty [11]. However, residents from both Treaty and non-Treaty villages frequently visit primary health facilities located on Australian islands in the TSPZ. Queensland Health triages both Australian and PNG nationals, from Treaty and non-Treaty villages, who present to a PHC within the TSPZ according to the nature and immediacy of the clinical presentation [12,13]. It is a national requirement for Australian health services to have systems in place to recognise clinical deterioration [14], and in the Torres Strait early warning tool scores are routinely used, with greater flexibility for Australian residents when additional diagnostic workup or treatment is required [15]. The majority of PNG nationals who present to a health facility in the Torres Strait are not critically ill and are referred back to the PNG health system, provided they have a stabilised medical condition prior to discharge [12]. Queensland Health makes no provision for preventative or chronic disease care, however, patients who are critically ill cannot be sent back and require aeromedical evacuation [12].

A triaging service is provided by clinicians in the Torres Strait. Wound care and pain medications are provided by PHC clinicians and on discharge additional supplies are dispensed to the patient [8]. Although it is not within Queensland Health's remit to invite PNG patients back for any follow-up care, laboratory results sharing, or treatment [13], in practice, frontline clinicians will often treat all PNG nationals, including repeated presentations. Anecdotally, this can include the administration of regular depot antipsychotics, which according to local policy would be considered a chronic condition for which treatment must not be provided [13]. It is unclear what the legal position is for limiting or denying health care from a human rights perspective given that the World Health Organization (WHO) International Health Regulations (2005) and United Nations Principles and Guidelines on Human Rights at International borders stipulate that health care may only be limited on significant public health grounds. As health care is not a provision of the Torres Strait Treaty, governance of health care at the border and associated moral responsibilities for PNG nationals and residents of the Torres Strait falls to Queensland Health and its frontline clinicians to navigate.

The Torres Strait is considered extremely remote by Australian standards and therefore does not have many of the health services afforded to residents of more populated areas [16]. Despite this, residents of the Torres Strait can access general outpatient care, with regular outreach clinics from visiting specialists and allied health services [17]. These services include vaccination, child and maternal health, sexual health, physiotherapy, mental health, and diabetes care [17]. Many PNG nationals living in the Western Province have limited access to health care infrastructure and have services that are often impacted by health worker shortages [18]. Inadequate healthcare availability is one of the reasons PNG

nationals in villages closest to the Australian border choose to access Australian healthcare services in the TSPZ [18]. The distance from PNG to the Australian PHC on Boigu Island in the Torres Strait is 4.7 kilometres, which is easily accessible in a 'dinghy' (small motorised boat). By comparison, the closest PNG hospital is located on Daru Island, which is a 2–4 h boat journey for residents from the Treaty villages closest to Australia [18].

The cost to provide outpatient care, aeromedical transfer, and inpatient management of a critically ill PNG TB patient from the Torres Strait Islands to Australian tertiary health facilities was recently reported as $124,280 (Australian Dollars) [19]. While the financial cost of aeromedical services is heightened by remote health care requirements, there are personal stakes for patients who present severely unwell, and for clinicians who are required to make difficult decisions regarding optimal treatment for these patients balanced against relevant government policies. In the Torres Strait/PNG border region, clinicians are expected to function in a complex health system environment limited by the scope of practice, available clinical tools, and spoken and unspoken policy and funding constraints [20]. There is difficulty in getting the 'balance' right between allowing humanitarian healthcare access, while limiting excessive healthcare expenses and supporting services in PNG. Delivering health care within the politically defined boundaries of the TSPZ may present additional challenges which may influence clinical decision-making and the care provided [21].

1.2. Management of PNG Nationals with TB

TB is a disease with a protracted natural history, which presents a major public health challenge in PNG, with particular concern about the transmission of highly drug-resistant strains in the Western Province [4]. Managing PNG nationals with possible TB in the TSPZ poses major clinical, logistical, ethical, political, and financial challenges at the interface of both jurisdictions. Patients requiring ongoing management and care are generally referred to Daru General Hospital in the Western Province of PNG. From October 2020, an upgraded health centre equipped with X-ray facilities opened for PNG patients at Mabadauan, a Treaty village adjacent to the Australian border [22].

As stipulated in the local Cross-Border Policy and Procedure documents for use on the Australian side of the border [12,13,23], clinicians need to complete patient observations (respiration rate, heart rate, oxygen saturation, blood pressure, temperature, level of consciousness, pain, and level of distress in paediatric patients) and document these in the relevant observations charts. The observation charts are known as the Queensland Adult Deterioration Detection Score (Q-ADDS), Children's Early Warning Tool (CEWT), and Queensland Maternity Early Warning Tool (QMEWT) [24]. There are four CEWTs and selection is dependent upon the age of the child presenting—<1 year, 1–4 years, 5–11 years and 12–17 years. Early warning tools are mandated in Queensland and are used to recognise and respond to clinical deterioration by tracking observations [25]. Each set of observations recorded is allocated a predetermined score on the chart, which allows clinicians to both predict/anticipate rapid deterioration and rapidly detect deterioration as it occurs, and identify the severity of illness. Based on these scores, the observation charts prompt the interventions required to manage each patient. Medical decisions are most often determined remotely by physicians (Rural Generalist Practitioners) based in Thursday Island Hospital. Where medical intervention fails to stabilise the patient and reduce the acuity of a PNG patient's presentation to a health facility in the outer Torres Strait Islands, an early warning tool score of $\geq$5 constitutes the criterion met for medical evacuation to an Australian hospital (Appendix 1 of the Cross Border Procedure [13]).

For patients with suspected TB that meet the aeromedical retrieval and transfer criteria, a negative pressure isolation room in an Australian hospital must first be identified before aeromedical evacuation can be arranged [23]. Most PNG patients that are medically evacuated are admitted to Thursday Island Hospital followed by a transfer to Cairns Hospital on the Australian mainland, once treatment for TB has commenced and the risk of infectivity is reduced. For the most complex and critically unwell patients, Thursday

Island Hospital is considered a staging area and transfer to Cairns or Townsville Hospitals should occur as soon as practicable [23].

Since the restructuring and strengthening of TB services located on Daru Island in PNG in 2012 [26], no evaluation has been done to explore access to TB care and outcomes achieved in PNG nationals presenting with presumptive TB to health services located in the Torres Strait Islands. This paper aims to provide an overview of the policy narrative at the Torres Strait/PNG border and examine the factors impacting patient care and outcomes. This paper will demonstrate how the tools available for clinical decision-making impact the clinical management of patients presenting with signs and symptoms of TB.

2. Methods

A retrospective audit of all PNG nationals who presented to Queensland Health facilities in the TSPZ with signs and symptoms of TB between 2016 and 2019, including those that were medically evacuated, was undertaken as part of this study. TB case notification data were obtained from Queensland Health's Notifiable Conditions System. Additional data sources used were patient charts, observation charts, Best Practice software, and the Excel spreadsheets used by the Torres and Cape TB Control Unit to record each health facility presentation of symptomatic PNG patients. The Torres and Cape TB Control Unit spreadsheets contain outcome data for PNG nationals referred back to the PNG health system, courtesy of shared data during visits by the Torres and Cape TB Control Unit to the TB Programme at Daru General Hospital or via correspondence with the Queensland Health Cross Border Communication Officer.

The WHO weight-for-age charts were used to identify if children fell beneath the 3rd percentile for age and weight [27]. PNG patients may be discharged if they can *be 'stabilised to the extent that no foreseeable deterioration will occur during return to the place of traditional inhabitation or to a health care facility outside of Australia'* and have a Q-ADDS/CEWT/QMEWT score $\leq$4 (Appendix 1 of the Cross-Border Procedure [13]). Therefore, the Torres and Cape Hospital and Health Service is obligated to ensure the patient receives care in an Australian hospital via aeromedical evacuation if the Q-ADDS/CEWT/QMEWT score is $\geq$5. Where early warning tool scores were not documented in observation charts or in Best Practice software, Q-ADDS, CEWT, and Q-MEWT, observation charts were used to manually calculate the score for each set of observations recorded.

Definition 1. *'$\leq$4' denotes patients that scored <5 on the Q-ADDS/CEWT/QMEWT which reflects local policy.*

Definition 2. *Age categories depicted in the results section were selected to reflect age categories used in the Q-ADDS/CEWT/QMEWT (<1; 1–4 years; 5–11 years; 12–17 years; $\geq$18 years).*

Descriptive statistics were generated using IBM SPSS Statistics, version 25 (2019, Armonk, NY, USA) and StataCorp, version 13 (Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.).

Existing clinical practice was benchmarked against local cross-border policy and procedures [12,13,23]. These are:

(1) Policy 0090-Papua New Guinea traditional inhabitants presenting to Queensland Health facilities within the Australian Islands of the Torres Strait Protected Zone;
(2) Procedure 1244-Management of Papua New Guinea traditional inhabitants presenting to Queensland Health facilities within the Australian islands of the Torres Strait Protected Zone;
(3) Procedure 0222-Management of Papua New Guinea Nationals accessing healthcare within the Australian Islands of the Torres Strait Protected Zone, presumed to have or diagnosed with Tuberculosis.

Patients were eligible if they presented to an Australian health facility in the TSPZ with suspected or confirmed TB, regardless of where or whether the diagnosis was confirmed [23].

Ethical approval was obtained from the Far North Queensland Human Research Ethics Committee (HREC/17/QCH/74-1157) and James Cook University (H7380). Patients were not involved in this study and a waiver of consent was granted by the Far North Queensland Human Research Ethics Committee (HREC/17/QCH/74-1157). Authorisation to use case notification data was granted under Public Health Act application QCH/36155-1157. The authors have conformed to the principles of the Declaration of Helsinki.

3. Results

Of 213 PNG nationals who presented to a PHC in the Torres Strait between 2016 and 2019 with signs and symptoms of TB, 44 (21%) were medically evacuated. Two PNG patients managed by Daru General Hospital were included in this audit because they initially presented to an Australian PHC with presumptive TB but were subsequently referred to Daru General Hospital by the Torres and Cape TB Control Unit. Another patient who presented with presumptive TB had been diagnosed with MDR-TB at Daru General Hospital prior to presenting to an Australian PHC. This patient was included in the audit because local procedures support the management of TB in patients with suspected or confirmed TB disease and the investigators decided to include known TB patients presenting emergently in the audit [23].

Of the 44 PNG patients with presumptive TB that were medically evacuated, 19 were diagnosed with TB. Table 1 shows that of 19 PNG patients diagnosed with TB that were medically evacuated, 10 had an initial score at the presentation of ≥5. Thirty-seven percent of TB cases medically evacuated were <18 years of age and of these; 57% fell beneath the third percentile for age and weight.

Figure 1 shows the outcomes of all PNG nationals who presented with signs and symptoms of TB. Of this group, 10 (4.7%) died within the follow-up period. Of the 10 patients who died, six were diagnosed with TB, and of the TB patients who died three were not medically evacuated. Of the included patient cohort, 48 PNG patients had an early warning tool score of ≥5 upon arrival of whom 5 (10.4%) died. Those with a score ≥5 on arrival were 3.7 times more likely to die (95% CI 1.1–12) than those with a score ≤4 on arrival. Of the 48 high-risk patients, 26 (54%) were medically evacuated to an Australian hospital. Of the remaining 22 patients who initially presented with an early warning tool score ≥5 and were not medically evacuated, 12 were discharged with a score ≥5; 8 arrived at Daru General Hospital, and 2 of these patients died, with 4 lost to follow-up.

Of 80 PNG patients aged <18 years that presented to a PHC in the Torres Strait between 2016 and 2019 with signs and symptoms of TB, 13 (16.3%) patients had an initial score of ≥5, and of those, 8 were medically evacuated into the Australian health system. A total of 29 (36.3%) patients aged <18 years fell under the third percentile for age and weight and, of those, 10 were medically evacuated. Five patients aged <18 years who were medically evacuated with an early warning tool score ≤4 fell beneath the 3rd percentile for age and weight.

In undertaking the audit, the terminology 'ceiling of care' was repeatedly observed in the Queensland Health software, Best Practice. Typically, 'ceiling of care' describes a discussion that medical officers have with patients and their families in the context of futility of care for terminally ill patients. Hence, a separate data query on the term 'ceiling of care' was run. Terminology 'ceiling of care' was identified eight times in PNG patient's Best Practice medical records, all of which were within this cohort and amounted to five PNG patients in total. A further PNG patient within the cohort had limitations on freedom of movement for healthcare applied but was not specifically labelled 'ceiling of care'. Of the six patients with a 'ceiling of care' or similar restriction, the majority had chronic neurological problems, but none had known terminal conditions. Four of these six patients were children, aged 12 months–16 years.

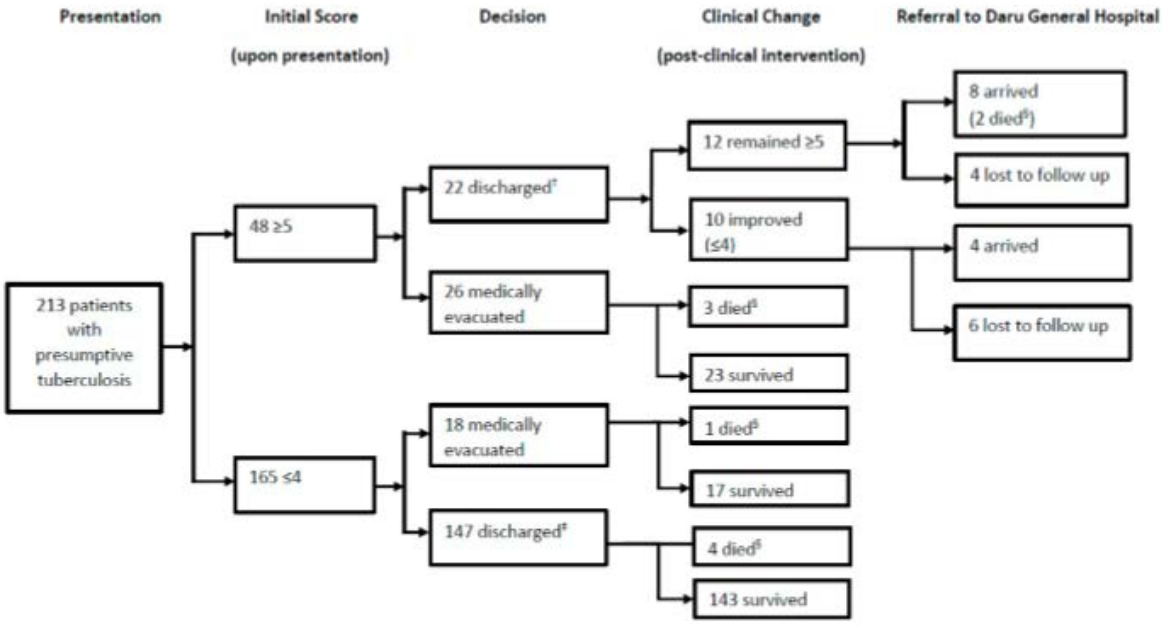

Figure 5.2.2 Outcomes of Papua New Guinea nationals who presented with presumptive TB to primary health centres in the Torres Strait, Australia, between 2016 and 2019 according to their early warning score

Table 5.2.1 Characteristics of Papua New Guinea nationals diagnosed with tuberculosis requiring aeromedical evacuation from the Torres Strait, Australia from 2016-20¬¬19 (N=19)

Characteristic	Hospitals Providing Care				
	Thursday Island Hospital *N* = 4	Thursday Island and Cairns Hospitals *N* = 12	Thursday Island and Townsville Hospitals *N* = 2	Thursday Island, Cairns, and Townsville Hospitals *N* = 1	Total *n* (%) (*N* = 19) †
Early warning tool score ≥5	1	7	1	1	10
Age, median (IQR) ‡					23 years (9–38)
Age group					
<1 year	0	1	1	0	2 (11)
1–4 years	0	1	0	0	1 (5)
5–11 years	1	2	0	0	3 (16)
12–17 years	0	1	0	0	1 (5)
18–29 years	0	4	1	0	5 (26)
30–44 years	3	0	0	1	4 (21)
≥45 years	0	3	0	0	3 (16)
Sex					
Female	1	6	1	1	9 (47)
Male	3	6	1	0	10 (53)

Table 5.2.1 *Cont.*

Characteristic	Hospitals Providing Care				
	Thursday Island Hospital $N = 4$	Thursday Island and Cairns Hospitals $N = 12$	Thursday Island and Townsville Hospitals $N = 2$	Thursday Island, Cairns, and Townsville Hospitals $N = 1$	Total *n* (%) ($N = 19$) †
Disease site					
Extrapulmonary	0	2	1	1	4 (21)
Pulmonary	4	8	0	0	12 (63)
Both XPTB and PTB	0	2	1	0	3 (16)
Drug resistance					
Clinical Dx only §	0	5	1	0	6 (32)
Fully drug susceptible	4	5	1	0	10 (53)
Multidrug-resistant	0	2	0	1	3 (16)

Note. XPTB—extrapulmonary tuberculosis; PTB—pulmonary tuberculosis; Dx—diagnosis; multidrug-resistant (TB which is resistant to both isoniazid and rifampicin). Note. Three patients with meningeal TB were managed at Townsville Hospital because it is the nearest facility with neurosurgery. † Represents 19 patients who were both diagnosed with tuberculosis and medically evacuated. ‡ Interquartile range. § No microbiological diagnosis.

4. Discussion

This study has identified inconsistent application of aeromedical retrieval policy, with patients not transferred for care despite meeting the criteria for medical severity and urgency. We report a range of poor outcomes in this cohort, including high mortality and loss to follow-up. Policy intended to avert such outcomes, particularly criteria for aeromedical retrieval to tertiary facilities, was not applied consistently. While our audit was not designed to explore the reasons for divergence from retrieval policy, our observations regarding the informal application of 'ceiling of care' without available documentation of reason for futility of care or case conference to discuss patient needs may indicate that such decisions are influenced by additional factors [28].

The pressures on clinicians to provide sound clinical judgment—often life and death decisions—while simultaneously avoiding costly care from patients who fall outside the Queensland Health remit, may lead to silent suffering and a risk burden on frontline clinicians that may be well beyond their training or experience [20].

There are many factors that lead to the high caseload in clinics in the Torres Strait Islands, Australia [2]. There is a significant discrepancy between healthcare services and outcomes on either side of the border of which Treaty villagers are well aware. Poverty and minimal preventative health activity in rural PNG leads to high rates of illness in residents of the Treaty villages. Travelling to Daru General Hospital for PNG Treaty villagers experiencing a health crisis or medical emergency can be prohibitive in terms of risk to life, personal safety, and personal costs [29].

Under the current system, once a decision on cross-border patient care has been made by the treating physician, there is no recourse to recall patients in need of further assessment or follow-up as per local policy 0900 and procedure 1244 [12,13]. Adding to the complexity of these care barriers are delays in transporting PNG patients from the Treaty villages to Daru General Hospital, with an average wait of 120 days between 2017 and 2018 [30]. Delays in transport for patients referred to Daru General Hospital pose an increased TB transmission and mortality risk in the region, while adding to Queensland Health expenses when patients represent.

Health service policy states that patients must be stabilised prior to discharge back to PNG and health care may only be withheld if treatment poses a substantial public health threat to community members (local policy 0900), in accordance with numerous statements on human rights [12,31,32]. As per local policy 0900, the costs of aeromedical evacuation and inpatient medical management should not guide clinical decision-making [12]. Despite this, medical decisions may be influenced by non-clinical factors, such as withholding care

due to high cost, which has been reported in other settings [33,34]. This study highlighted that in the Torres Strait Islands, the phrase 'ceiling of care' may be used to mitigate other factors, such as cost or responsibility the health service takes for PNG nationals. As identified in the audit, in the Torres Strait, 'ceiling of care' is being used to indicate to other staff the limits that are to be placed on care such as fluid, inotropic agents or antibiotics, or restrictions of movement, such as the location in which the care stops. We did not investigate consent or whether decisions to limit care were unilateral as has occurred in other settings [35] but found no evidence in medical records of consent or multi-disciplinary conferences in decision-making.

PNG nationals who live across this border are 'liminal'—existing in the space between—with both rights and restrictions placed on them by Australia [36]. There are, however universal human rights that apply regardless of political agreements, and it is contingent on these services to provide emergency care consistent with human rights. The liminal nature of PNG residents living adjacent to the Torres Strait Islands places a moral burden on healthcare workers to make determinations about the standard of care that will be provided. To avoid this burden being unreasonable, it must be consistent and transparent, both for the sake of PNG residents and for the healthcare decision-makers. We clearly risk harm to the PNG residents by denying needed care and by arbitrarily doing so. It may be less clear but also important that we also risk moral injury to decision-makers if we put them in a conflicted position regarding such choices, particularly where there are not transparent and objective criteria to guide them [37]. Monitoring and enforcement of standards is also a protection for healthcare decision-makers.

Early warning tools (Q-ADDS, CEWT and QMEWT) used in Queensland Health alert clinicians to vital signs of concern, using a colour-coded scoring system [25]. These tools are valuable in detecting severe bacterial sepsis or other emergent conditions likely to cause death; however, they were not developed to detect serious diseases relevant to the region including malnutrition and TB. In this study, 40% of patients that died having presented with signs and symptoms of TB were discharged back to PNG with an early warning Tool score $\leq$4. Conversely, 41% of patients who were medically evacuated had a score $\leq$4. Therefore, the scoring systems used may not be sufficiently sensitive to identify the most serious case presentations. For example, early warning tools do not allocate points to critical pathology results, and a patient with TB and pancytopenia may be discharged on a score $\leq$4 even though the patient may be experiencing a life-threatening medical emergency [38]. Further, the early warning tools do not allow for any allocation of points for failure to thrive or severe malnutrition, which are prominent features in paediatric patients with TB in PNG and can lead to rapid deterioration [39]. Using generic deterioration scores has been shown to decrease sensitivity to life-threatening conditions, particularly when used in specialty areas of care [40].

This study was unable to fully identify on which basis clinical decisions were made to either refer PNG patients presenting to Australian PHCs back to the PNG health system or to medically evacuate them to an Australian hospital. Further information about care provided to PNG patients, outcomes for those referred back to the PNG health system, and information on the cause of death for those patients who subsequently died is needed to identify the spectrum of patients' outcomes following clinical decisions made at the time. Further research is warranted to better assist clinicians working in this complex context to optimise clinical decisions and patient outcomes.

Patient review is an essential element of the management of acute presentations to ensure patients can be safely discharged from care. Without the possibility of patient follow-up and with very low rates of post-mortem coroner referrals or referral pathways and feedback, some decisions are made without necessary oversight, transparency, or health system support.

Implementation of local policy and procedures pertaining to the management of PNG nationals presenting to health facilities in the Torres Strait were formulated, in part, to reduce ambiguity and to provide clarity for remote area clinicians on the appropriate

management of patients. Aeromedical evacuations are necessary to provide equitable access to people with critical medical needs in remote settings, but this comes at substantial cost to the health system [41]. The very high costs of care are well known to clinicians who must make individual decisions under uncertainty, placing a burden on themselves and potentially leading to a reluctance to medically evacuate, consequently leading to reduced care in some cases, with cost to patients. In view of our findings, Box 1 summarises some key recommendations.

Box 1. Key recommendations for improving care for patients with presumptive tuberculosis presenting to health facilities in the Torres Strait, Australia.

1. Orientation and training of all staff is required to adequately address complex operational challenges associated with remote health care delivery, including ethical and medico-legal issues associated with time-critical health emergencies [42];
2. In addition to the identification of patient deterioration using current early warning tool scores, implementation of clinical algorithms that are appropriate for TB patients and malnourished children is warranted [43];
3. Exploring factors that influence both nurse's and physician's responses to patient deterioration is required, including how peer-modelling may improve health care delivery and adherence to policy [44,45];
4. Ongoing monitoring and evaluation to ensure transparency and justice is required [46]. Outcomes shared with local stakeholders will promote greater transparency of decision-making, with rapid identification of skills shortages and deviations from policy or policy limitations and with continuous service improvements led by frontline nurses and clinicians [46];
5. Care pathways that include documenting a set of vital signs just prior to discharge and with a medical review for Q-ADDS/CEWT/QMEWT scores ≥5 may improve patient outcomes and visibility of deviating vital signs [47]. An automated notification within the existing health system software may be beneficial to (a) prompt clinicians to collect and record vital signs at discharge and (b) reduce deviations from policy and procedures [48];
6. Greater transparency into how 'ceiling of care' decisions are made for cross border PNG patients seeking healthcare via the TSPZ is required.

Note. Ceiling of care—describes a discussion that medical officers have with patients and their families in the context of futility of care for terminally ill patients; however, in this study, 'ceiling of care' was applied to PNG patients who did not have known terminal conditions.

While TB causes a substantial number of deaths in PNG, determining the cause can be difficult due to concurrent health conditions and a lack of access to autopsy services [49]. In this study, the cause and the timing of death were unknown for some cases. In some instances, it is unknown if death occurred during or before treatment commencement. Further, the Q-ADDS/CEWT/QMEWT score was not available at the time of discharge for all patients; hence the last recorded set of vital signs were used in this study.

5. Conclusions

While more effective and efficient models of care are being developed in the Western Province in PNG, it is likely PNG nationals with presumptive TB will continue to present at Australian clinics in the Torres Strait. Risk scoring tools that are not appropriately contextualised may limit the accurate identification of serious cases requiring aeromedical evacuation. Tools that can perform both initial triage and identify subsequent deterioration in TB patients are required. Tools that incorporate a longer timespan for potential deterioration are needed in view of the high rates of loss to follow-up and slow arrival to Daru General Hospital. In the meantime, consistent use of the best available tools will reduce the burden of responsibility on frontline health workers involved in the remote management of these patients and support medical decision-making that is transparent and committed to equity.

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Informed Consent Statement: Patients were not involved in this study and a waiver of consent was granted by the Far North Queensland Human Research Ethics Committee (HREC/17/QCH/74-1157).

Data Availability Statement: As notifiable disease data have been used in this study, public sharing of data is restricted due to confidentiality clauses. Access to data requires Human Research Ethics Committee, Public Health Act and Site-Specific Access approvals via Queensland Health.

Conflicts of Interest: J.F. and E.S.M. are employees of the Torres and Cape Tuberculosis Control Unit. D.P. is an employee of Tropical Public Health Services Cairns and works in the Torres Strait/PNG border region as the Cross Border Communication Officer.

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Note: James Cook University required the removal of some data within this publication, as a pre-condition for my PhD award. This was done to satisfy all thesis requirements, but my supervisory team and article co-authors feel that "the removal of Papua New Guinean people who have died during a medical episode constitutes erasure and is deeply disrespectful to these people and their communities" (personal communication, co-author JD, 25.09.24).

Figure 6.1 Child with TB/malnutrition (Foster, 2019; with consent).

Chapter 6: Critical review of tuberculosis diagnosis in children from Papua New Guinea presenting to health facilities in the Torres Strait Islands, Australia

Overarching Aim #2: Identify opportunities for evidence-based enhanced policy and practice for the management of TB in the region (Translational Research).

Overarching Aim #3: Identify opportunities for strengthened cross-border communication and collaboration between Australia and PNG health services to better manage TB in the region.

Overarching Aim #5: Compare Torres Strait paediatric TB diagnostics with international methods to improve child TB detection.

Aims:

1. To review all case data of paediatric patients with TB and presumed TB.
2. Examine current deterioration detection scoring tools used and their impact on paediatric patients with presumed TB.
3. Examine outcomes in paediatric patients that presented with signs and symptoms of TB to the TSPZ.

In this paper, I determine that the Torres Strait / PNG border region is using diagnostic methods that are insufficient to identify all cases of paediatric TB. I compare the Keith Edwards TB Score, the Union's Desk Guide and the new World Health Organization algorithm, and benchmark diagnostic scores against existing diagnostic systems available. Outputs of the analyses are that 1) local TB physicians may have been over-diagnosing lymph node TB but underdiagnosing paediatric TB overall; 2) the best diagnostic agreement was observed between the Union's Desk Guide and the new World Health Organization algorithm, indicating that modifications to existing diagnostic systems based on these two approaches may increase diagnostic yield in children; 3) approximately half of all paediatric patients were undernourished at the time of presentation. Of children locally diagnosed with TB that were undernourished, 90% had severe acute malnutrition and 4) greater attention to paediatric malnutrition may increase diagnostic yield and reduce paediatric TB-related mortality.

6.1 Publication and outputs for Chapter 6

I was the lead author of the following paper. My contribution to the study and subsequent outputs were as follows:

- I developed the concept for this study.
- I contributed to the design of this study.
- I wrote the ethics application for this study.
- I wrote the Public Health Act authorisation application for this study.
- I collected the data for this study.
- I attended a number of workshops about how to conduct quantitative research via the Doctoral Cohort Program at JCU.
- I used Excel and SPSS to organise the data collected and attended to all coding.
- I conducted the analysis with results reviewed by my supervisory team.
- I was the lead author of the manuscript which I initially drafted.
- I managed the submission of this manuscript which is pending peer-review.

6.1.1 Translation Research

- I met with all staff of the Torres and Cape Tuberculosis Control Unit to discuss the findings of the study. I subsequently implemented a change to local procedure, whereby paediatric patients aged under 12 years have their middle upper arm circumference measured. This additional measurement is now also available for children over 12 years when clinicians suspect malnutrition. This has allowed TB physicians additional data to determine the likelihood of a paediatric TB diagnosis.
- I intend on using the findings of this study to implement the following post-doc: 1) design, pilot then validate a paediatric scoring system that is workable in the Torres Strait, lending from a range of different tools available and working with measurement parameters in place or than can easily be introduced; 2) integrate the current medivac scoring system used and add additional scores that translate into medivac criteria for paediatric patients with presumptive TB and 3) prospectively collect data from paediatric patients to obtain paediatric MUAC and age/weight that may allow for a baseline of malnutrition in this population.

Results from this study are included in the following peer-reviewed publication.

Critical review of tuberculosis diagnosis in children from Papua New Guinea presenting to health facilities in the Torres Strait Islands, Australia

J'Belle Foster., Ben J Marais., Diana Mendez., Emma S McBryde

Abstract

Background: Paediatric tuberculosis (TB) can be challenging to diagnose and various approaches are used in different settings. The aim of this study was to benchmark existing diagnostic practices used in the Torres Strait against internationally recognized approaches and the new World Health Organization (WHO) evidence-based algorithm.

Methods: We undertook a retrospective analysis of Papua New Guinea (PNG) children who presented to health facilities in the Torres Strait Protected Zone with presumptive TB between 2016 and 2019. We assessed agreement between the different diagnostic approaches, including the modified Keith Edwards TB Score, The Union Desk Guide and the new WHO algorithm.

Results: In total, 66 children presented with presumptive TB; seven were diagnosed with bacteriologically confirmed TB. Most (52%) children were less than 5 years (median age 61 months) and 45% were undernourished (weight-for-age <3rd percentile). There was fair agreement between the different diagnostic approaches (K=0.34; 95% Confidence Interval [CI] 0.23 - 0.46) with the best agreement between The Union Desk Guide and the new WHO diagnostic algorithm (K=0.61).

Discussion: Compared with other diagnostic approaches, diagnosis by TB physicians may have over-treated presumed lymph node TB, but under-treated TB overall. Improving the accuracy and timeliness of paediatric TB diagnoses through pragmatic tools is critical to reduce TB-related mortality in children, especially in remote settings like the Torres Strait and the Western Province of PNG.

Acknowledgements

We thank all children who contributed data to this analysis. We thank Professor Steve Graham and Dr Dunstan Peniyamina who critically reviewed the manuscript and Dr Chris Coulter for reviewing five chest X-rays. We also thank Geraldine Sullivan for the graphic design in Figures 6.1.2 and 6.1.3.

Key Findings:

- Paediatric TB is difficult to diagnose and remains a major concern at this international border.
- The new World Health Organization Paediatric TB algorithm was published at the time the study took place and to the best of our knowledge, this study is the first in the Western Pacific region to investigate its utility in recognising paediatric tuberculosis.
- In this study, we identified that 90% of children diagnosed locally with TB had severe acute malnutrition.
- We also identified that the absence of a local diagnostic algorithm may have led to over-diagnosing lymph node TB but under-diagnosing paediatric TB overall.

Key Implications:

- Programmatic management of TB in the region could be improved by specific tools that can be practically implemented and perform well in the context of the Torres Strait / PNG international border region.
- This study both identifies a subset of patients at increased risk and demonstrates a need to reduce the likelihood of missed diagnoses.
- Fit-for-purpose diagnostic algorithms that are specific to the paediatric population, inclusion of anthropometric measurements in TB screening tools and associated policy, and training of primary healthcare centre clinicians in fine needle aspiration biopsy to diagnose lymph node TB will be critical adjustments needed to improve detection of paediatric TB in this region.

Background

Tuberculosis (TB) is recognised as a top ten cause of under-5 mortality in TB endemic areas, such as Papua New Guinea (PNG).[1] Approximately 10% of all TB cases diagnosed are in children aged <15 years.[2] While children with TB are generally less contagious than adults, their mortality risk is higher, especially in the very young and immunocompromised.[3] Active TB disease typically develops in children within the first 12 months after exposure and primary infection.[4] An estimated 90% of children who die from TB, die without ever being diagnosed or accessing TB treatment and care.[5]

Persistent gaps in TB case detection in children result from the pauci-bacillary nature of their disease and their inability to expectorate sputum.[6] Microbiological confirmation takes up to six weeks, yields are low and specimen collection is difficult. In the absence of more advanced diagnostic options, pragmatic diagnostic approaches such as scoring tools and algorithms may assist with diagnosis in children and improve their access to treatment and care.[7]

PNG residents from Treaty villages in the Western Province of PNG can access basic diagnostic and referral services via Australian health facilities in the Torres Strait (Figure 6.1.1). Typically, bacteriologic studies available for these children were limited to voluntary expectoration, nasopharyngeal aspirates in outpatient settings, nasogastric aspirates in inpatient settings, and rarely, sputum induction. Once diagnosed with presumptive TB in the Torres Strait, PNG patients must then access TB services located on Daru Island in the Western Province of PNG, to commence treatment. In PNG's Western Province, the estimated TB incidence rate is very high (736/100,000 population in 2017)[8] and nearly a third (27%) of TB case notifications are in children <15 years of age.[9]

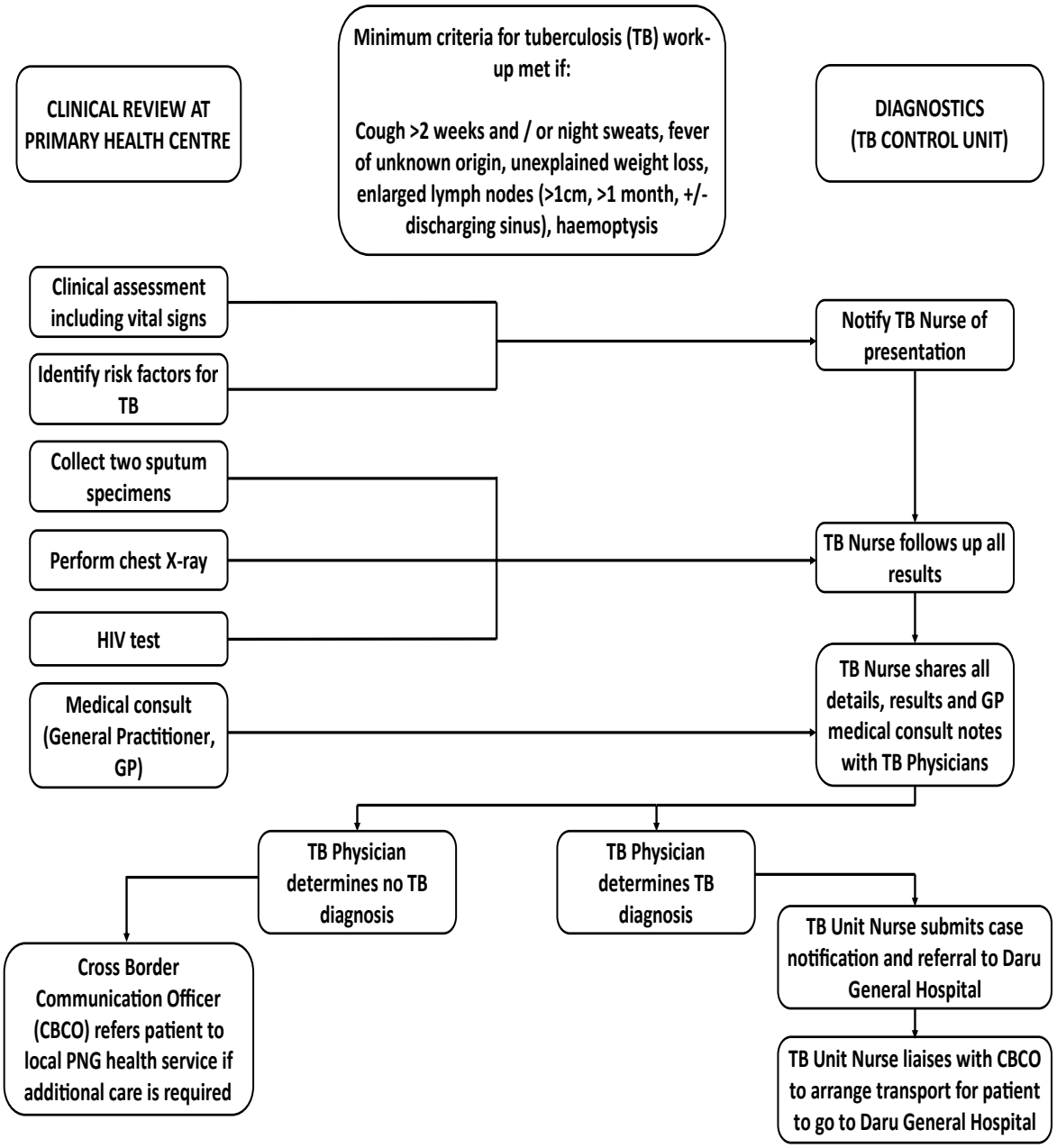


Figure 6.1.1 Diagnostic work-up for patients from Papua New Guinea visiting health services in the Torres Strait Protected Zone

To date, no validated TB diagnostic tool or algorithm has been used in the Torres Strait to assist TB triage or diagnosis in children. The use of symptom-based clinical diagnostic approaches in remote settings are supported by both the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease (The Union)[10,11] to reduce TB-related mortality and enable children to enter the TB care pathway sooner. We aimed to compare current paediatric TB diagnostic approaches used in the Torres Strait, with three internationally recognised approaches – 1) the Keith Edwards Score developed in PNG (1987)

(Figure 6.1.S1)[12]; 2) The Union Desk Guide, 3rd edition (2016) (Figure 6.1.S2) [10]; and 3) the new WHO evidence-based paediatric TB algorithm (2022) (Figure 6.1.S3).[13]

Methods

We performed a retrospective study including all paediatric patients (aged 0-14 years) from PNG that presented with presumptive TB to a Queensland Health facility in the Torres Strait Protected Zone between January 2016 and December 2019. TB case definitions included bacteriologically confirmed or clinically diagnosed TB cases.[14] Sites of TB disease included pulmonary, extra-pulmonary, or both. The study excluded children who resided in the Torres Strait, since their data was captured by a separate system for Australian residents.

Diagnostic work-up of PNG nationals at health facilities in the remote Australian Torres Strait Islands is usually triggered when a child presents with at least one sign or symptom suggestive of TB.[14] TB work-up and specimen collection is performed in close consultation with a rural General Practitioner (GP) who provide a dedicated outreach service.[14]

Patient charts and data on all presumptive TB cases among PNG nationals contained in the electronic database used in the Torres and Cape Hospital and Health Service, called Best Practice, were accessed. Chest X-ray (CXR) results were obtained from Queensland Health's radiological software (PACS) and pathology results from Queensland Health's laboratory information system called AUSLAB.

Weight loss was based on subjective reports of recent loss of weight by patient's parents or care givers. The WHO online weight-for-age calculator was used to manually calculate weight-for-age percentiles for the purpose of this study.

Diagnostic approaches

1. *Clinical decision made by local Physician*

Diagnostic practices in the region were based on the presence of clinical features of disease and epidemiological risk factors, and the results of diagnostic investigations following the clinical algorithm in Figure 6.1.1.[15]

Unfortunately, local policy prevents recalling PNG patients across the international border for any purpose, including tuberculin skin test (TST) reading, repeat CXR, or review following a

course of antibiotics or nutritional rehabilitation.[16] Health services rendered to presumptive TB patients who are in a 'non-critical' condition, are provided with the specific purpose of identifying TB and referring patients back to the PNG health system for ongoing care.[17] Australia has made significant investments to support quality TB care on Daru Island, which is on the PNG side of the border.[18]

2. Keith Edwards TB Score

The Keith Edwards TB Score (Figure 6.1.S1) was developed in PNG and a score of ≥7 indicates a high likelihood of paediatric TB.[12,19] Two data points included in the Keith Edwards TB Score namely TST reading and malnutrition with failure to improve after four weeks of nutritional rehabilitation (collectively worth six points), were not collected in our setting and had to be excluded from this study.

We modified three data points in the original Keith Edwards TB Score (1987) for use in this study (Table 6.1.S1) to overcome issues associated with locally-derived data. The Keith Edwards TB Score specifies points allocation for nutrition status (no points for patients >80% of expected weight for age, one point if 60-80% and three points if <60% of expected weight for age).[19] We used WHO weight-for-age percentile charts up to 10 years of age, and the WHO weight-for-age calculator, and adjusted the criteria as follows: no points if ≥15th percentile, one point if 3-14th percentile and three points if < 3rd percentile. Further, no points are allocated in the Keith Edwards TB Score to patients with no family history of TB, one point if contact with sputum smear negative TB and three points if contact with sputum smear positive TB.[19] As patients presenting to health facilities in the Torres Strait rarely knew if TB contacts were sputum smear positive or negative, we allocated two points for known TB contact, irrespective of sputum smear status. When the duration of fever or night sweats was recorded as ≤2 weeks, no points were allocated and 2 points were allocated if >2 weeks.

3. The Union Desk Guide

The Union Desk Guide (2016) (Figure 6.1.S2) requires persistent signs and symptoms of TB to be present.[10] Patients with signs and symptoms of ≤2 weeks were excluded from a possible positive diagnosis and enlarged lymph nodes were allocated one point (Table 6.1.S1). The Union Desk Guide recognises microbiologically confirmed (we included all culture positive cases) and clinically diagnosed cases. A clinical TB diagnosis requires at least two of three features to be present where one point is allocated against each; 1) close contact with a known

case, 2) signs and symptoms of TB and 3) a CXR suggestive of TB. Therefore, the maximum number of points that could be allocated in this study was four, inclusive of laboratory-confirmation.

All CXR reports written by a radiologist were reviewed and a point allocated for any parenchymal opacification or cavity, miliary lesions, intrathoracic lymphadenopathy or when the radiologist indicated that the CXR was suspicious for TB. Where the radiologist indicated an abnormality in the report but where there was limited description, a TB Specialist (B.J.M. or C.C.) reviewed and reported on whether the abnormality was TB-related.

4. New WHO Paediatric TB algorithm

WHO recently published consolidated new evidence-based guidelines on the treatment and care of TB in children,[20] in conjunction with a detailed operational handbook.[13] The operational handbook contains a new evidence-based algorithm to improve TB case detection in high burden settings.[13] The algorithm (Figure 6.1.S3) focuses on practical treatment guidance in children <10 years with presumptive pulmonary TB, and accepts relatively low specificity to ensure a sensitivity of at least 85%. Entry into the algorithm requires the presence of suspicious pulmonary signs and symptoms for a minimum duration of 1-2 weeks. Vulnerable children, defined as those aged <2 years, with severe acute malnutrition and / human immunodeficiency virus (HIV), do not have to meet minimum criteria for entry into the algorithm if they are contacts of known cases (Figure 6.1.S3). Past this point, the algorithm then allocates points to other suspicious signs and symptoms including enlarged lymph nodes and suggestive CXR changes (if CXR is available) with a score >10 indicating a need for treatment.

Some modifications had to be made to the new WHO algorithm due to data limitations (reflected in Table 6.1.S1). Progression through the algorithm requires that some 'low risk' patients be followed up in 1-2 weeks to assess persistent or worsening symptoms. Apart from high-risk patients (aged <2 years and <3rd percentile for age/weight), children required >2 weeks of signs and symptoms to be assessed. As time since exposure to a known TB case is not recorded in the Torres Strait, any close contact of a known TB case was assessed instead of only those exposed in the past 12 months.

In the absence of height and growth trajectory data, severe acute malnutrition was defined as weight-for-age Z-score of more than 2 standard deviations below the mean which was a weight-

for-age percentile of ≤0.00%. Patients with weight <3rd percentile for age were considered to have a suggestive sign of TB.[13]

Analyses

Frequencies and proportions were calculated using SPSS (version 28; New York, 2021). The Pearson's chi square test was used to determine the association between select characteristics.

Fleiss' kappa was used to assess agreement between the four different TB diagnostic approaches evaluated. Standard kappa tests were used to measure individual agreement between each of the approaches.

Ethical clearance and a waiver of consent was obtained from Far North Queensland Human Research Ethics Committee (HREC/17/QCH/74-1157), and James Cook University (H7380). All data were obtained with approval from data custodians within Queensland Health and with Public Health Act authorisation (QCH/36155 – 1157).

Results

Table 6.1.1 reflects the demographics and other characteristics of the 66 PNG children, aged between 3 months and 14 years, who presented with signs and symptoms of TB to an Australian health facility in the Torres Strait. Of these, 21 (32%) were diagnosed with TB by local TB physicians. The majority of children (34/66; 52%) evaluated were <5 years of age, including 12/21 (57%) diagnosed with TB. Of 65 children that were weighed, 29/65 (45%) children were <3rd percentile for age and weight. Using WHO weight-for-age percentiles in 10 patients diagnosed locally with TB in this study, 90% (9/10) of those that fell beneath the third percentile were identified as having severe acute malnutrition defined as a weight-for-age percentile of ≤0.00%.

Table 6.1.1 Characteristics of Papua New Guinea children who presented to health facilities in the Torres Strait Protected Zone with presumptive tuberculosis (2016-2019)

Characteristic	TB treatment advised N = 66 (%)		
	Yes	**No**	**Total**
Age group (median 61 months)			
<5 years	12 (35)	22 (65)	34 (52)
5-9 years	5 (29)	12 (71)	17 (26)
10-14 years	4 (27)	11 (73)	15 (23)
Sex			
Female	9 (29)	22 (71)	31 (47)
Male	12 (34)	23 (66)	35 (53)
Visa Status			
Papua New Guinea Treaty Visitor	17 (30)	39 (70)	56 (85)
Papua New Guinea non-Treaty Visitor	4 (40)	6 (60)	10 (15)
Primary Health Centre Attended			
Saibai	18 (33)	37 (67)	55 (83)
Boigu	3 (33)	6 (67)	9 (14)
Other	0 (0)	2 (100)	2 (3)
Recent close contact of a known TB case			
Close contact	11 (42)	15 (58)	26 (39)
No close contact	10 (25)	30 (75)	40 (61)
Chest x-ray (CXR) ^			
CXR performed	18 (34)	35 (66)	53 (80)
CXR not performed	3 (23)	10 (77)	13 (20)
Nutritional status			
<3rd percentile for age and weight	10 (34)	19 (66)	29 (44)
Severe acute malnutrition	9 (90)	7 (37)	16 (55)
TB signs and symptoms*			
Cough >2 weeks	7 (28)	18 (72)	25
Fever	14 (26)	40 (74)	54
Night sweats	7 (37)	12 (63)	19

Characteristic	TB treatment advised N = 66 (%)		
	Yes	**No**	**Total**
Weight loss	10 (33)	20 (67)	30
Enlarged lymph nodes[#]	11 (44)	14 (56)	25
Haemoptysis	1 (100)	0 (0)	1

^ CXR – chest radiograph

Note. * Signs and symptoms as reported by the parent or care giver, each patient may have more than one sign or symptom recorded; [#] defined as >1cmx1cm for >1 month, +/- discharging sinus

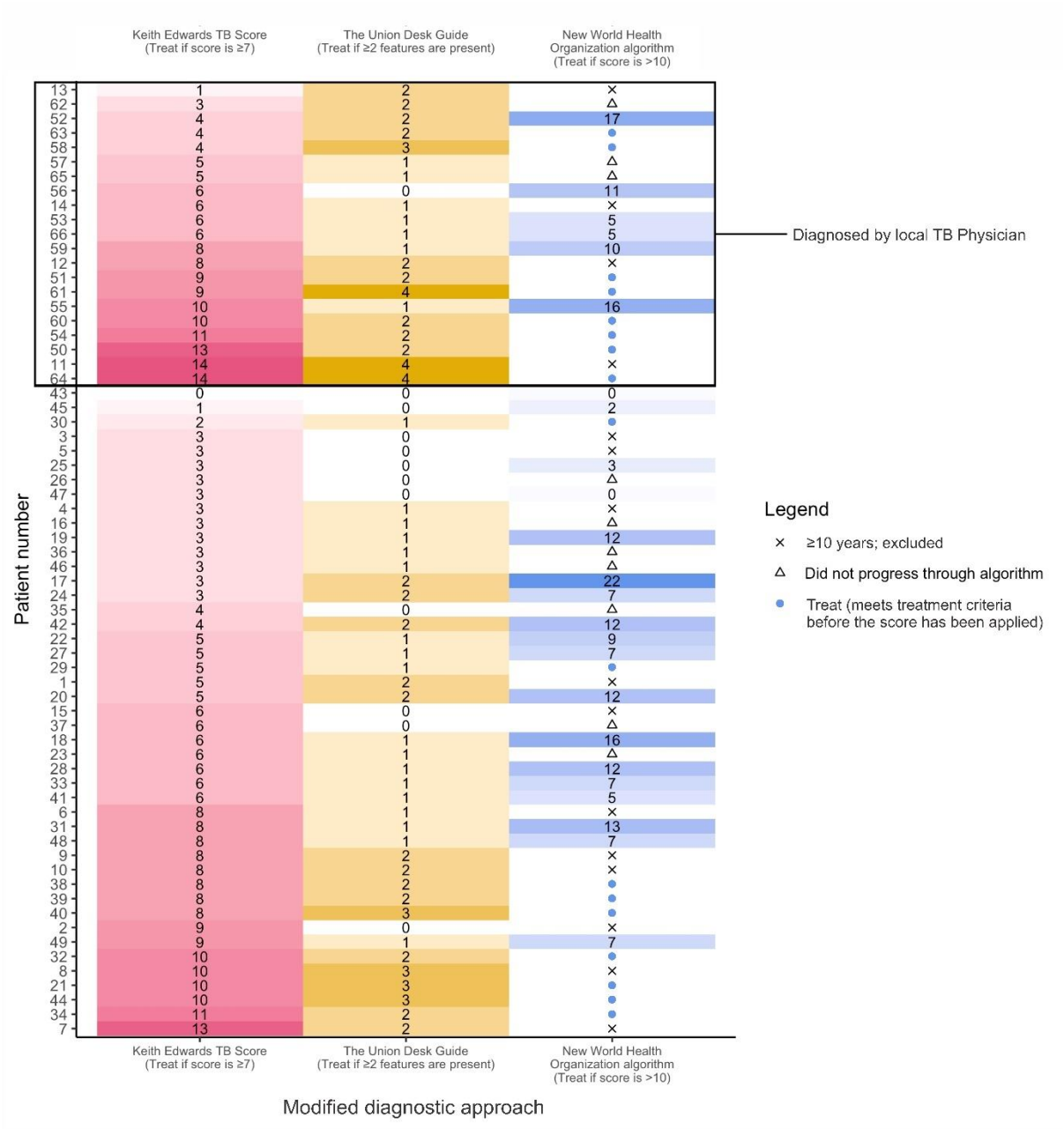
No child tested HIV positive (0/27 tested). Only one child had received a Bacille Calmette-*Guérin* (BCG) vaccine. The most common presenting symptoms were fever (54/66; 82%) and cough (47/66; 71%). Of those with a cough, 25/47 (53%) coughed for >2 weeks. Of the 21 patients treated for TB, 7/21 (33%) had microbiological confirmation; two with confirmed multidrug-resistant (MDR) TB. None of the six patients diagnosed with lymph TB had a fine needle aspiration performed.

Table 6.1.2 shows the level of agreement between the four diagnostic approaches evaluated. Overall, there was fair agreement between the specified diagnostic approaches (K=0.34; 95% Confidence Interval [CI] 0.23 - 0.46), with the best agreement between The Union Desk Guide and the new WHO algorithm (K=0.61; p <.001). Figure 6.1.2 reflects individual patient level agreement between the different diagnostic approaches, demonstrating variable agreement.

Table 6.1.2 Individual agreement between local Physician's TB diagnoses, the Keith Edwards TB score, The Union Desk Guide, and the new World Health Organization algorithm for the diagnosis of paediatric TB.

		New World Health Organization algorithm					Union Desk Guide					Keith Edwards TB Score				
		Not TB	TB*	Total	K	p	Not TB	TB*	Total	K	p	Not TB	TB*	Total	K	p
Local TB Unit	**Not TB**	18	16	34	0.15	0.2	29	16	45	0.24	**0.045**	29	16	45	0.11	0.4
	TB	6	11	17			8	13	21			11	10	21		
	Total	24	27	51			37	29	66			40	26	66		
New WHO algorithm	**Not TB**	NA	NA	NA	NA	NA	22	2	24	0.61	**<0.001**	21	3	24	0.42	**0.001**
	TB	NA	NA	NA	NA		8	19	27			12	15	27		
	Total	NA	NA	NA	NA		30	21	51			33	18	51		
Union Desk Guide	**Not TB**	22	8	30	0.61	**<0.001**	NA	NA	NA	NA	NA	30	7	37	0.47	**<0.001**
	TB	2	19	21			NA	NA	NA	NA		10	19	29		
	Total	24	27	51			NA	NA	NA	NA		40	26	66		

Overall agreement (K=0.34; 95% Confidence Interval [CI] 0.231 - 0.46; $p<0.001$)
K - Cohen's kappa value; TB - tuberculosis; WHO - World Health Organization
*'TB' refers to 'guidance to treat for TB', not microbiological confirmation or any other objective reference standard

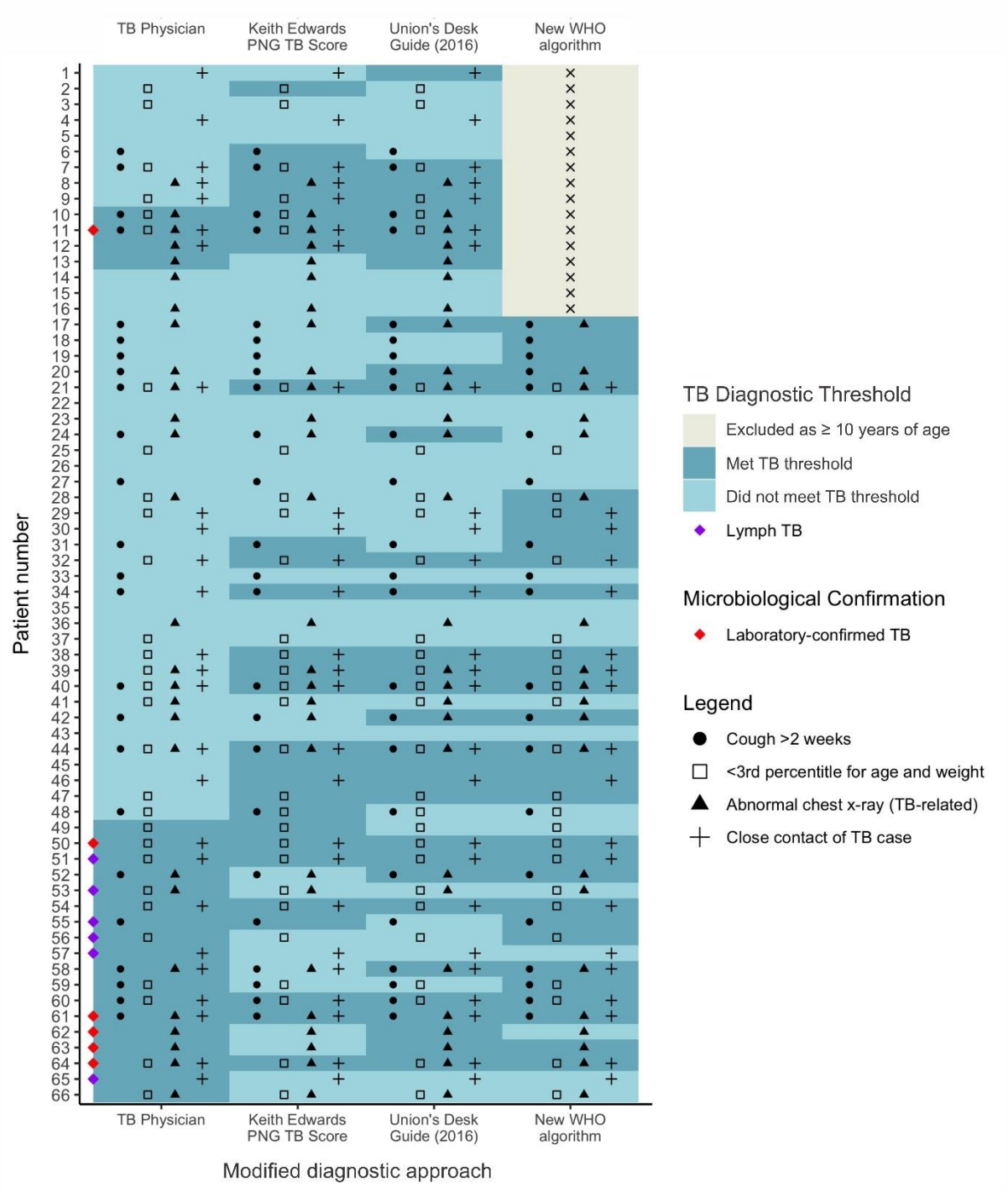


TB, tuberculosis.

Figure 6.1.2 Illustration of individual level agreement between local TB Physicians' diagnoses, and the modified Keith Edwards TB score, The Union Desk Guide, and the new World Health Organization algorithm

Figure 6.1.3 provides a detailed description of individual features documented in children with presumptive TB. The modified Union Desk Guide correctly identified all seven cases with microbiologically confirmed TB, compared to the modified Keith Edwards TB Score that correctly identified four cases. Of the five cases aged <10 years that were diagnosed with microbiologically-confirmed TB, four were identified as requiring TB treatment by the new

WHO algorithm. The remaining case did not have persistent symptoms suggestive of pulmonary TB and was not considered a 'vulnerable child' and therefore did not progress through the diagnostic pathway. More paediatric TB cases were diagnosed using the Keith Edwards TB Score, (26), the Union Desk Guide (29) and the new WHO algorithm (27), than were diagnosed by local TB Physicians (21). When applying the modified scores, 19 (Keith Edwards TB Score), 15 (Union Desk Guide), and 14 (new WHO algorithm) would have been diagnosed. Of six lymph node TB cases diagnosed by a local TB Physician, consensus was only achieved across all diagnostic approaches for one case, acknowledging that the new WHO algorithm specifically focuses on pulmonary TB in children.



PNG, Papua New Guinea; TB, tuberculosis; WHO, World Health Organization
Note. TB threshold refers to 'guidance to treat for TB'; not microbiological confirmation or any other objective reference standard

Figure 6.1.3 Detailed description of individual features documented in children with presumptive TB comparing local Physicians' diagnoses, and the modified Keith Edwards TB score, The Union Desk Guide, and the new World Health Organization algorithm

Discussion

Overall, our study demonstrated that the new WHO algorithm was more inclusive than other diagnostic approaches, although one culture-confirmed case was not detected. In the absence of a defined reference standard, we are not able to comment on diagnostic accuracy, but the highest agreement was observed between The Union Desk Guide (2016) and the new WHO algorithm, is that there is an urgent need to improve children's TB treatment access, especially in high TB incidence settings, in order to reduce TB-related mortality.[21-23] Although some over-treatment is preferable in some high TB incidence settings to under-treatment, clinicians in the Torres Strait need to find a difficult balance between timely TB diagnosis and not referring cases to the PNG health system unnecessarily.[14]

Increased case notifications may lead to higher costs to individual patients and health systems.[24] We conservatively modified each tool to fit with available diagnostic infrastructure in the Torres Strait. Our modifications generally led to lower scores, but even after modification more cases were diagnosed using each of the three diagnostic approaches than those diagnosed by local TB Physicians. Each of the algorithms could be applied in the Torres Strait Islands, but restricted access to patients for follow up and limited laboratory diagnostic support should be considered. CXR is readily available on two Australian islands close to the PNG border, but the quality and cost are variable, while wide interobserver variability limits its use as a reference standard.[6] Nasopharyngeal or nasogastric aspiration and induced sputum collection is not always available[25] and is dependent upon the skillsets of local nurses and clinicians. Similarly, specimens required for an extra-pulmonary TB diagnosis such as pleural fluid or lymph node aspirates are not typically collected in the Torres Strait. In this study, more than half of all cases diagnosed locally had extra-pulmonary TB involvement, and of those, 55% were diagnosed with cervical TB lymphadenitis.

Enlarged cervical lymph nodes due to TB can be confused with many other causes, including cancer,[26] which is why fine needle aspiration biopsy (FNAB) is such a valuable tool to confirm the correct diagnosis and ensure appropriate treatment. FNAB of cervical lymph nodes that are persistent and greater than 1x1cm is an underutilized, but safe and simple diagnostic modality that can enhance diagnostic accuracy.[27] The sensitivity and specificity of FNAB to establish a TB diagnosis is excellent[28] and yields with Xpert MTB/RIF® or Ultra® are good.[27] Training and implementation of FNAB and access to Xpert MTB/RIF® or Ultra® could improve

diagnostic accuracy,[29] but the time delay in establishing a diagnosis if specimens need to be sent away remains problematic when dealing with cross-border patients.

According to PNG health statistics, 24% of children are underweight and 14% are potentially at-risk of death due to moderate or severe forms of malnutrition.[30] These figures may be a result of poor caloric intake and due to the consequences of poverty such as poor sanitation and hygiene.[31]

Both the new WHO algorithm and the Union Desk Guide work optimally with access to longitudinal growth data to ascertain 'failure to thrive.' 'Failure to thrive' is a measure of inadequate weight gain and growth over time[32] and as there is a no recall policy in place at the Torres Strait / PNG border, identifying 'failure to thrive' or monitoring weight over time is not possible for PNG nationals presenting to a healthcare facility in the Torres Strait.

WHO age-for-weight percentiles and anthropometric measurements such as weight-for-height (BMI) and middle upper arm circumference (MUAC), are not routinely calculated for paediatric patients presenting with presumptive TB in the Torres Strait. Low BMI and MUAC have been shown to be predictors of both TB mortality[33] and TB disease, and both have shown to improve with TB treatment.[34]

A child with a BMI Z-score of >3 standard deviations below the mean of WHO growth standards, or a MUAC <115 mm (6-59 months) or <130 mm (5-9 years) indicates severe acute malnutrition with increased mortality risk.[35,36] Of the 29 children who presented with malnutrition, TB was in 10 patients, demonstrating the high yield of TB detection among severely malnourished children in TB endemic settings. Similar findings have been reported in African studies.[37-39] Where high yield of TB and high prevalence of severe acute malnutrition coexist, TB screening should include a malnutrition assessment. A shift in policy to enable these diagnostic pathways, in the same way TB screening automatically follows a HIV diagnosis and vice versa[23] is indicated and is likely to improve the management and outcomes of paediatric TB in these regions.

Together with improved uptake of BCG vaccination, improved strategies to address malnutrition may be a valuable primary TB prevention strategy in this setting. In the interim, routine monitoring of nutritional status and key malnutrition datapoints such as weight and MUAC should be incorporated into existing policies and procedures to provide critical triage points[40] for improved TB screening.[41]

Some important study limitations require consideration. As described above, due to the retrospective nature of the study, all three of the diagnostic algorithms used in this study needed to be modified. This is because TB management in the Torres Strait is limited by borderlands regulation, high staff turnover limiting the ability to implement a consistent and sustainable source of TST providers in remote primary healthcare settings and a lack of advanced point of care diagnostic technology such as the Xpert MTB/RIF® or Ultra®. A further limitation of the study is that we did not collect outcome data on patients and as such, were unable to report on local mortality risks associated with TB and malnutrition. These limitations highlight the difficulty of cross border evaluation. A strength of the study is that it included all patients that presented with signs and symptoms of TB during the study period.

Conclusion

Diagnosing paediatric TB in remote settings without the possibility of recall across an international border is challenging. High rates of malnutrition and low BCG vaccination coverage are major concerns in paediatric patients from PNG presenting to health facilities in the Torres Strait.

Reducing the likelihood of missed diagnoses and time to effective treatment commencement requires further exploration of optimal diagnostic approaches in this setting. Implementing modified components of these algorithms that are suitable and have shown good discrimination in this context as part of a prospective operational research project, may provide such an opportunity.

Supplementary Materials

TABLE 1. Keith Edwards Score for Diagnosis of Tuberculosis in Children

Feature	Score		
	0	1	3
Duration of illness (weeks)	< 2	2-4	> 4
Nutrition (% of weight for age)	> 80	60-80	< 60
Family history of tuberculosis	None	Reported by family	Proven sputum positive

Score for Other Features if Present

Feature	Score
Unexplained fever, night sweats, no response to malaria treatment	2
Positive tuberculin test	3
Lymph nodes: large, painless, firm, soft sinus in neck/axilla	3
Malnutrition, not improving after 4 weeks	3
Central nervous system : change in temperament, fits with or without abnormal cerebrospinal fluid findings	3
Joint swelling, bone swelling, sinuses	3
Unexplained abdominal mass, ascites	3
Angle deformity of spine	4

A score of 7 or more is indicative of tuberculosis

Figure 6.1.S1 Keith Edwards Score for Diagnosis of Tuberculosis in Children 1987[12]

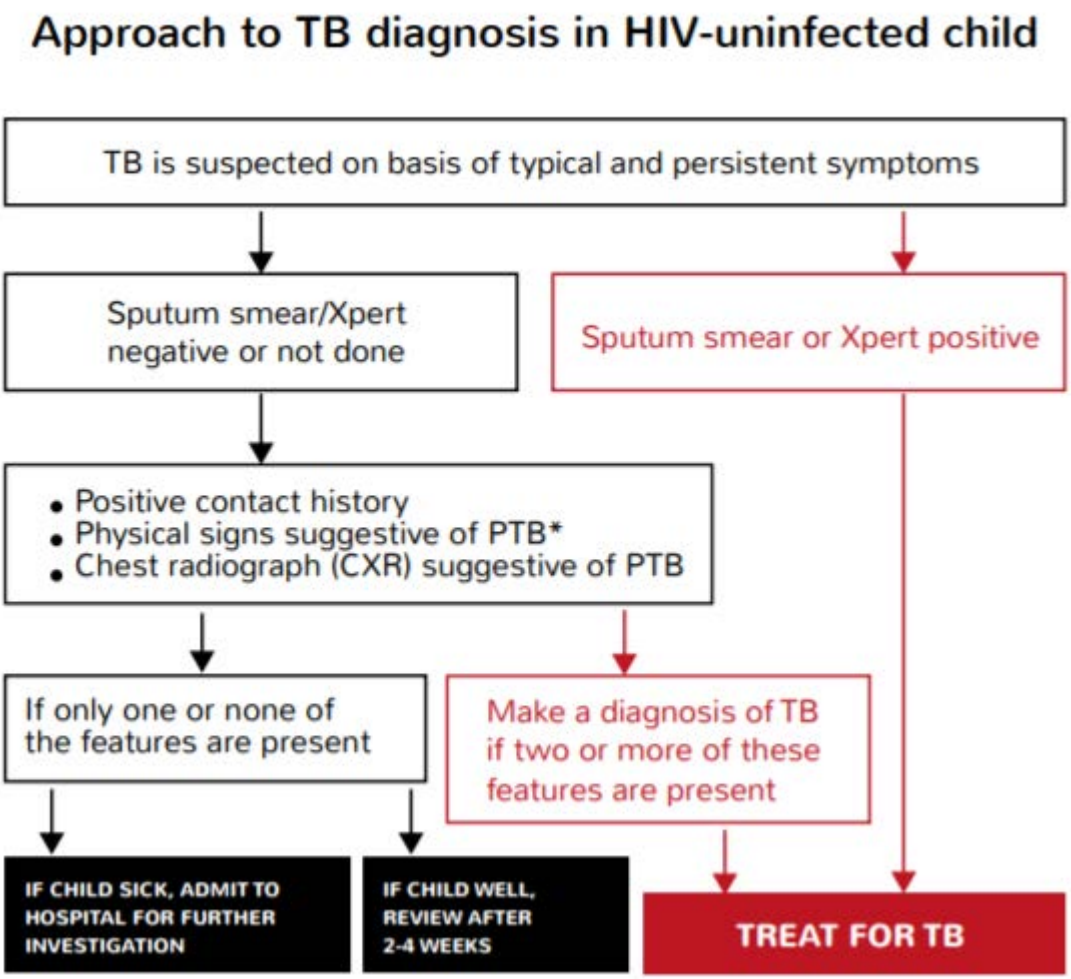


Figure 6.1.S2 The Union Desk Guide 3rd Edition 2016[10]

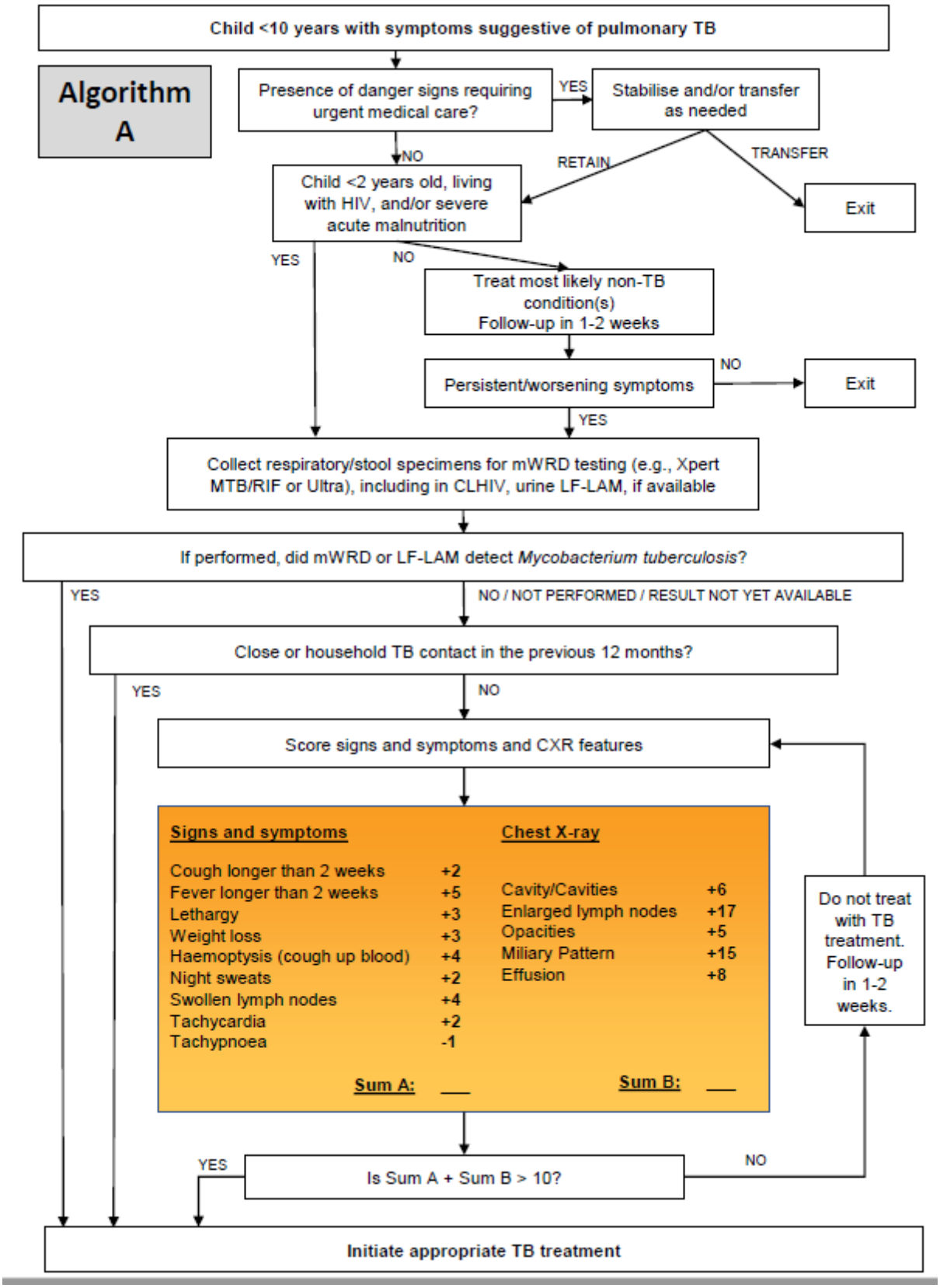


Figure 6.1.S3 New World Health Organization Paediatric TB algorithm 2022[13]

Table 6.1.S1 Description of established and modified scoring in Keith Edwards TB Score, The Union Desk Guide and the New WHO Algorithm

	KEITH EDWARDS TB SCORE (1987)	MODIFIED KEITH EDWARDS TB SCORE	UNION DESK GUIDE (2016)	MODIFIED UNION DESK GUIDE	NEW WHO ALGORITHM (2022)	MODIFIED WHO ALGORITHM
DIAGNOSTIC FEATURE	**SCORING SYSTEM (POINTS-BASED)**		**DIAGNOSTIC GUIDE**		**OPERATIONAL ALGORITHM**	
COUGH	0 - <2 weeks 1 – 2-4 weeks 3 - >4 weeks	0 - <2 weeks 1 – 2-4 weeks 3 - >4 weeks	0 – ≤2 weeks 1 – >2 weeks	0 – ≤2 weeks 1 – >2 weeks	0 – ≤2 weeks 2 – >2 weeks	0 – ≤2 weeks 2 – >2 weeks
FEVER	0 - <2 weeks 1 – 2-4 weeks 3 - >4 weeks	0 – ≤2 weeks 2 – >2 weeks	0 – ≤2 weeks 1 – >2 weeks	0 – ≤2 weeks 1 – >2 weeks	0 – ≤2 weeks 5 – >2 weeks	0 – ≤2 weeks 5 – >2 weeks
WEIGHT LOSS	3 - malnutrition not improving after four weeks of nutritional rehabilitation	Excluded **	0 – not reported 1 – reported	0 – not reported 1 – reported	0 – not reported 3 – reported	0 – not reported 3 – reported
NIGHT SWEATS	0 - <2 weeks 1 – 2-4 weeks 3 - >4 weeks	0 – ≤2 weeks 2 – >2 weeks	0 – ≤2 weeks 1 – >2 weeks	0 – ≤2 weeks 1 – >2 weeks	0 – not reported 2 – reported	0 – not reported 2 – reported

	KEITH EDWARDS TB SCORE (1987)	MODIFIED KEITH EDWARDS TB SCORE	UNION DESK GUIDE (2016)	MODIFIED UNION DESK GUIDE	NEW WHO ALGORITHM (2022)	MODIFIED WHO ALGORITHM
DIAGNOSTIC FEATURE	**SCORING SYSTEM (POINTS-BASED)**		**DIAGNOSTIC GUIDE**		**OPERATIONAL ALGORITHM**	
SWOLLEN LYMPH NODES	0 – not present 3 – present	0 – not present 3 – present	Not specified	0 – not present 1 – present	0 – not reported 4 – reported	0 – not reported 4 – reported
TB CONTACT	0 – no family history of TB 1 – contact with sputum smear negative TB 3 – contact with sputum smear positive TB	0 – no family history of TB 3* – known TB contact of either sputum smear positive or negative	0 – no TB contact history 1 – TB contact history	0 – no TB contact history 1 – TB contact history	0 – no TB contact history in previous 12 months 0 – TB contact history in previous 12 months without persistent symptoms Treat - TB contact history in previous 12 months with persistent symptoms	0 – no TB contact history in previous 12 months 0 – TB contact history in previous 12 months without persistent symptoms Treat - TB contact history in previous 12 months with persistent symptoms
WEIGHT-FOR-AGE (WFA)	0 - >80% expected WFA 1 - 60-80% WFA	0 - ≥15th WFA percentile 1 - 3-14th percentile	N/A	N/A	Severe Acute Malnutrition – eligible to progress	< 3rd percentile - eligible to progress to through until the end of the algorithm

	KEITH EDWARDS TB SCORE (1987)	MODIFIED KEITH EDWARDS TB SCORE	UNION DESK GUIDE (2016)	MODIFIED UNION DESK GUIDE	NEW WHO ALGORITHM (2022)	MODIFIED WHO ALGORITHM
DIAGNOSTIC FEATURE	**SCORING SYSTEM (POINTS-BASED)**		**DIAGNOSTIC GUIDE**		**OPERATIONAL ALGORITHM**	
	3 - <60% WFA	3 - < 3rd percentile			to through until the end of the algorithm	
HIV	N/A	N/A	N/A***	N/A	HIV positive - eligible to progress to through until the end of the algorithm	HIV positive - eligible to progress to through until the end of the algorithm
TB INFECTION	3 – positive tuberculin skin test	Excluded	N/A	N/A	N/A	N/A
CHEST X-RAY FINDINGS	N/A	N/A	0 – Not suggestive of TB or nor done 1 – Suggestive of TB	0 – Not suggestive of TB or nor done 1 – Suggestive of TB	0 – Not suggestive 6 – Cavities 17 – Enlarged lymph nodes 5 – Opacities 15 – Miliary pattern 8 – Effusion	0 – Not suggestive 6 – Cavities 17 – Enlarged lymph nodes 5 – Opacities 15 – Miliary pattern 8 – Effusion

	KEITH EDWARDS TB SCORE (1987)	MODIFIED KEITH EDWARDS TB SCORE	UNION DESK GUIDE (2016)	MODIFIED UNION DESK GUIDE	NEW WHO ALGORITHM (2022)	MODIFIED WHO ALGORITHM
DIAGNOSTIC FEATURE	**SCORING SYSTEM (POINTS-BASED)**		**DIAGNOSTIC GUIDE**		**OPERATIONAL ALGORITHM**	
SPECIMEN FOR SMEAR/XPERT	N/A	N/A	0 – Sputum smear/ Xpert negative or not done 1 – Sputum smear or Xpert positive	0 – Sputum smear/ Xpert/culture negative or not done 1 – Sputum smear/ Xpert/culture +	0 – Sputum smear/ Xpert negative or not done Treat – Sputum smear or Xpert positive	0 – Xpert/culture negative or not done Treat - Xpert/culture positive
CNS	3	3	N/A	N/A	N/A	N/A
SKELETAL	3	3	N/A	N/A	N/A	N/A
ABDOMINAL	3	3	N/A	N/A	N/A	N/A
ANGLE DEFORMITY OF SPINE	4	4	N/A	N/A	N/A	N/A
SCORE INTERPRETATION	Treat if score is ≥7		Treat if ≥2 features are present		Treat if score is >10	

CNS: Central nervous system: change in temperament, fits +/- abnormal cerebrospinal fluid findings
Skeletal: Joint swelling, bone swelling, sinuses
Abdominal: Unexplained abdominal mass, ascites

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Figure 7.1 Torres and Cape Hospital and Health Service TB Unit building dumped on the side of a hill on Thursday Island during hospital renovations (Foster, 2021).

Chapter 7: Discussion and Conclusion

Aims:

1. Demonstrate how each study in the thesis linked with the themes identified in the scoping and narrative reviews and how the overall aims of the thesis have been addressed.
2. Provide an integrated synthesis with high level critical analysis, interpretation of findings and their implications for clinical practice.
3. Demonstrate how advancement of knowledge has enhanced clinical practice (translational research).
4. Provide recommendations for future research.

7.1 Aims of the thesis

Aim 1 →

Investigate cross-border tuberculosis (TB) disease epidemiology

Review and synthesize current evidence and new data to explore historical and current TB management of residents of the Torres Strait Islands and PNG nationals accessing TCHHS facilities in the Torres Strait Protected Zone (TSPZ) to provide an understanding of disease epidemiology.

Aim 2 →

Identify opportunities for evidence-based enhanced policy and practice for the management of TB in the region (Translational Research)

Explore policy and practice of TB services, and how these shape TB management in the Torres Strait / PNG international border region. Provide locally-derived evidence to support new approaches to improve the management of all patients with presumptive TB and active TB disease in this region.

Aim 3 → **Identify opportunities for strengthened cross-border communication and collaboration between Australia and PNG health services to better manage TB in the region**

To identify opportunities to strengthen engagement between TB programmes in the Torres Strait Islands and Daru Island, PNG.

Aim 4 → **Assess the aeromedical evacuation efficiency for TB in the Torres Strait and evaluate decision-making for PNG nationals with presumptive TB at the Australia / PNG border**

Investigate the efficiency and outcomes of aeromedical evacuation processes for TB management in the Torres Strait Islands and evaluate the decision-making consistency and equity for PNG nationals with presumptive TB presenting at the Australia / PNG international border.

Aim 5 → **Evaluate and compare the current paediatric TB diagnostic methods in the Torres Strait against internationally recognised approaches to enhance timely and effective TB diagnosis in children.**

Compare Torres Strait paediatric TB diagnostics with international methods to improve child TB detection.

The aims of this thesis were: 1) Identify cross-border TB disease epidemiology; 2) Identify opportunities for evidence-based enhanced policy and practice for the management of TB in the region (translational research); 3) Identify opportunities for strengthened cross-border communication and collaboration between Australia and PNG health services to better manage TB in the region; 4) Assess the aeromedical evacuation efficiency for TB in the Torres Strait and evaluate decision-making for PNG nationals with presumptive TB at the Australia / PNG border and 5) Compare Torres Strait paediatric TB diagnostics with international methods to improve child TB detection. These aims align with the World Health Organisation's (WHO)

End TB Strategy which is anchored on three key "Pillars and Components".[1] Pillar one centres on integrated, patient centred TB care and prevention. Pillar two calls for bold TB-related policies and supportive systems. Pillar three focusses on the intensification of TB research and innovation.

This thesis adds to the knowledge base on TB management and has enabled greater understanding of the epidemiological profile of TB in the Torres Strait / PNG cross-border region. TB patient services are predominantly provided via primary health centres (PHCs) located on remote islands and as such, implementation of Pillar one of the WHO End TB Strategy requires a baseline epidemiological profile of the disease in this region to enhance integrated and patient-centred care.[1] The programmatic challenges and effects of both clinical and programmatic decisions over time, as described in this thesis, have shown that TB control goes beyond the biomedical model of diagnosing and treating the disease alone. This thesis has shown that delivering patient care in the Australia / PNG cross-border region requires policies, procedures, tools, and health systems that both support the complexities, and the decision makers at the frontline. Although this thesis highlighted some major past deficits in the care of presumptive and active TB patients, which could be perceived by some as cause for an insurmountable crisis of conscience, it also provides opportunities to turn deficits into future benefits. The evidence derived from this thesis will pave the path to better meet the WHO End TB Strategy's call to action for bold TB-related policies.

This thesis has demonstrated that there is room for innovation and opportunity for collaborative efforts between health services on both sides of the border. As the Torres and Cape TB Control Unit shares many of the same patients with the Daru TB Programme, evidence within this thesis can now support new approaches through collaborative action and research.

This doctoral thesis aimed to explore the epidemiological profile of residents of the Torres Strait Islands and PNG nationals presenting to health services in the Torres Strait with presumptive and active TB disease. The collection and synthesis of new data, and the resulting research findings have provided a new body of evidence to better support programmatic management of TB services in the Torres Strait region. This research has contributed to conceptual and methodological understanding of TB in the region and has the potential to influence future health care provision, policy and practice for TB services in the Torres Strait.

This thesis also aimed to add to the existing body of evidence by examining the epidemiological profile of TB in the Torres Strait / PNG border population to inform changes to local policy that will result in improved patient outcomes, lives saved, improved diagnostics, increased collaboration and better overall management of TB in the region. As previously outlined, in Queensland, the Torres Strait Islander population is disproportionately affected by TB as a result of close geographical proximity and cultural connections to Treaty villages in the Western Province of PNG where TB is endemic.

This doctoral thesis was undertaken with the specific purpose of gathering evidence that would have the greatest impact on future programmatic management of TB for Indigenous Australians and PNG nationals living adjacent to the Torres Strait. Prior to conducting this research, there was little published literature describing predictors of transmission risk or programmatic insights for this cross-border population. There were previous descriptive studies of routinely collected surveillance data available, which either focused on TB in PNG nationals or included TB in residents of the Torres Strait Islands, but rarely covered both populations, both health systems and the impact of public health responses on both sides of the border.

Each study in this thesis was carefully and deliberately selected to enable grassroots improvements at the coal face of TB management in the region. Decisions were made with the purpose of prioritising programmatic needs that required sufficiently robust evidence to enable interventions that could be rapidly and/or sustainably implemented to improve TB control in the region, hence many of the research findings generated throughout this PhD have already resulted in changes to policy and practice.

This thesis is comprised of nine distinct studies:

1. a scoping review of TB management-related challenges from a global perspective
2. a narrative review of the history of TB management in Northern Australia and in the Torres Strait / PNG international border region
3. a comparative study of pulmonary TB (PTB) diagnostic yield from two and three sputum specimens
4. spatiotemporal analyses of the rise of TB drug-resistance at the Australia / PNG border and identification of predictors of different types of mono and multidrug-resistance
5. time to event analyses to determine effective treatment commencement delays over time

6. identification of factors contributing to unfavourable outcomes in patients diagnosed with drug-resistant TB
7. a case study and descriptive costings of the aeromedical and medical management of a TB patient from PNG
8. descriptive analyses and critical examination of clinical deterioration scores and adherence to local policy in relation to determining eligibility for aeromedical evacuation for patients with presumptive TB and
9. comparative study of current paediatric diagnostics versus three modified TB diagnostic scoring systems used in other settings

The introductory chapter (Chapter 1) of this thesis included a scoping review to ascertain global challenges to managing TB (Figure 7.1.1) followed by a narrative review of the historical management of TB in Northern Australia and a description of the management of TB in the cross-border region (Figures 7.1.2 and 7.1.3). The aim was to establish a baseline for existing published literature on TB in the region, augment it with programmatic observations globally and within the Torres Strait / PNG cross-border context, and identify gaps in the knowledge base. Although the scoping review in Chapter 1 focused on the depth and breadth of available literature, there was a paucity of literature on TB in the Torres Strait / PNG border region, where much of what was available was based on crude numbers or descriptive studies. Chapter 2 described how data for this thesis were collected as well as the challenges of collecting data in a biosecurity zone. Chapters 3 to 6 set out to examine data that had the potential to impact policy decisions and improve the management of TB in the region. Chapter 3 supported existing policy decisions and illustrates areas for improvement in specimen collection and management. In Chapter 4, molecular epidemiology was used to make inferences about whether changes to programmatic management of TB over time contributed to better patient outcomes. Chapter 4 was comprised of three studies and one descriptive paper that focuses on the distribution and predictors of drug-resistant TB. Chapter 5 illustrated the financial, ethical and practical challenges of existing policy and procedures and further identifies gaps in the clinical management of cross-border TB patients. Chapter 6 identified deficits in diagnosing paediatric TB in remote settings. Table 7.1.1 shows how each of the eight studies (some published; others pending publication) link in with the thesis aims and the themes identified in the scoping and narrative reviews.

Table 7.1.1 The main focus of the eight studies and linkages with themes identified in the scoping and narrative reviews and overall aims of the thesis

Paper	Context & Research Output	TB Management Aspect	Translational Research	Type of Paper	Theme/s	Aim
1	Diagnostic yield Title: *TB in the Torres Strait: The Lady Doth Test Too Much* (Published)	Diagnostics PTB	Yes	Original research	Treatment delay Clinician education Limited laboratory support in remote settings Policy implications Climatic challenges Cross-border management/control of TB	1 2 3
2	Geospatial mapping and predictors of DR-TB Title: *Spatiotemporal trends of drug-resistant TB in the Torres Strait Islands, Australia and Papua*	DR-TB	Yes	Original research Spatial analysis	Cross-border management/control of TB	1

Paper	Context & Research Output	TB Management Aspect	Translational Research	Type of Paper	Theme/s	Aim
	New Guinea border region between 2000 and 2020 (In review)					
3	Cross-border management of TB Title: *Cross-border tuberculosis: opportunities, challenges and change* (Published)	Multidrug-resistant TB (MDR-TB)	No	Conceptual Descriptive	Geographic challenges Cross-border management/control of TB	1
4	Total effective treatment commencement delay Title: *Time to commencement of effective treatment in patients with drug-resistant tuberculosis diagnosed in the Torres*	Drug-resistant TB (DR-TB)	Yes	Original research	Treatment delay Cross-border management/control of TB	1 3

Paper	Context & Research Output	TB Management Aspect	Translational Research	Type of Paper	Theme/s	Aim
	Strait/Papua New Guinea cross-border region (Published)					
5	Predictors of unfavourable outcome Title: *Predictors of unfavourable outcome in patients diagnosed with drug-resistant tuberculosis in the Torres Strait/Papua New Guinea border region* (Published)	DR-TB	Yes	Original research	Comorbidities Disrupted health services Access issues Geographic challenges Poor nutrition Clinician education Cross-border management/control of TB	1 2 3
6	Cost to manage TB patients Title: *Cost of tuberculosis-related aeromedical retrievals in the Torres Strait, Australia*	PTB	No	Original research Cost analysis	Allocation of financial resources Geographic challenges Policy implications Cross-border management/control of TB	2 4

Paper	Context & Research Output	TB Management Aspect	Translational Research	Type of Paper	Theme/s	Aim
	(In review)					
7	Ethical implications of cross-border TB care Title: *Critical consideration of tuberculosis management of Papua New Guinea and cross-border health issues in the remote Torres Strait Islands, Australia* (Published)	Diagnostics	Yes	Original research	Policy implications Access issues Clinician education Cross-border management/control of TB	2 3 4
8	Diagnosing PNG nationals with paediatric TB Title: *Critical review of tuberculosis diagnosis in children from Papua New Guinea presenting*	Diagnostics	Yes	Original research	Treatment delay Policy implications Limited laboratory support in remote settings Cross-border management/control of TB	2 3 5

Paper	Context & Research Output	TB Management Aspect	Translational Research	Type of Paper	Theme/s	Aim
	to health facilities in the Torres Strait Islands, Australia (In review)					

Figure 7.1.1 Key themes (blue) identified in Chapter 1, part 1 - Scoping review (managing TB under challenging circumstances – lessons from international settings).

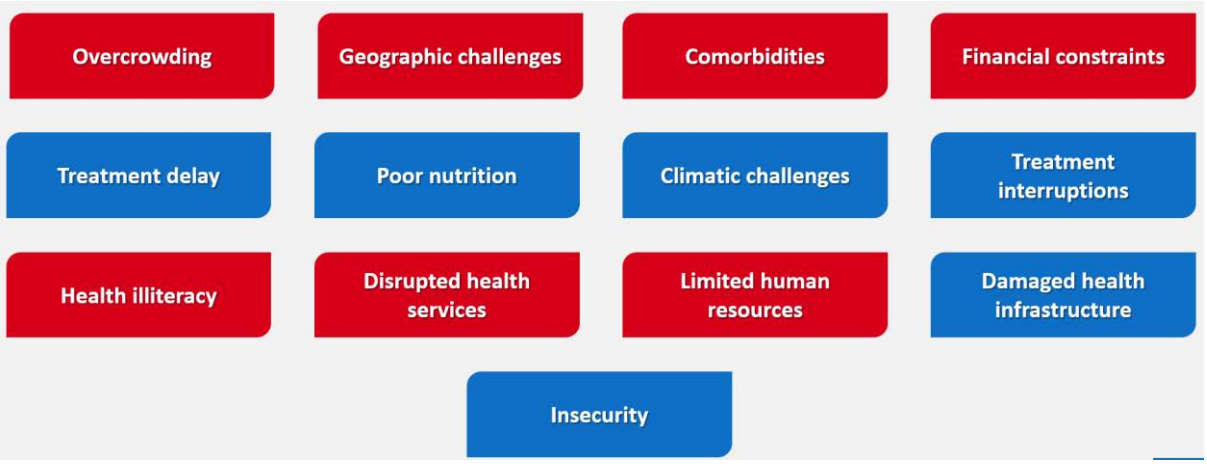


Figure 7.1.2 Key themes (red) identified in Chapter 1, part 2 - Managing tuberculosis in Northern Australia, Torres Strait and Papua New Guinea (previous findings and observations from the region).

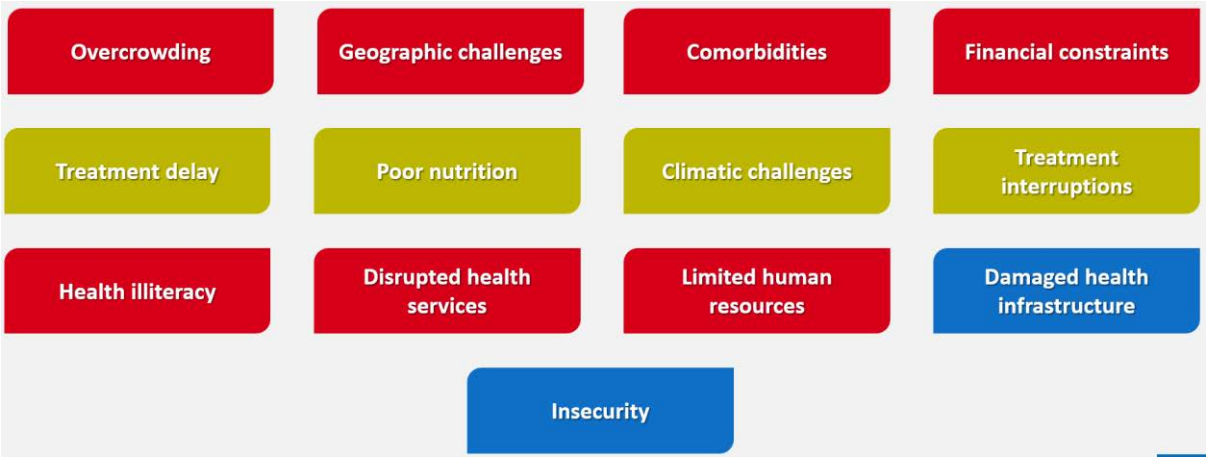


Figure 7.1.3 Key themes (mustard) identified during data interrogation and clinical experiences in the region.

7.2 How did the findings relate to the literature?

With the exception of damaged health infrastructure and insecurity, each theme played a role but not all themes were included in the thesis. Of the 11 themes that were relevant to Managing TB in Northern Australia, eight were included in the thesis (Figure 7.1.4).

Figure 7.1.4 Key themes (red and mustard) included in thesis.

7.3 Limitations

7.3.1 Researcher bias

As I am both a researcher and policy writer in this specific field and location, the introduction of researcher bias was therefore unavoidable. Pre-research bias is present in every study in this thesis as a result of selecting studies that would enable the best understanding of the epidemiological profile of TB in the region relevant to TB control priorities, or where findings

would contribute to changes in programmatic management. However, it should be noted that bias was introduced only during the research planning stage, and did not impact on statistical analyses used to compile data and establish the validity and reliability of research findings.

7.3.2 Sample size limitations

Each dataset created and used in this thesis were subject to sample size issues. As there was no selection bias in these studies, and every patient that met inclusion criteria was included in each study, there was no opportunity to increase the sample size during this research. This means that all our findings are representative and generalisable to the Torres Strait / PNG border population with presumptive or diagnosed TB. There were however, some examples within the thesis where sample size likely impacted the findings. For example, as nearly every patient in the dataset used for drug-resistant TB analyses had low haemoglobin levels, and previous studies have indicated a significant association between anaemia and unfavourable outcomes in TB patients, it is likely that a type II error occurred as there was insufficient statistical power to expose an effect. This limitation may be overcome in the future by the incorporation of both drug-resistant and DS-TB patients in analyses.

7.3.3 Methodological limitations

Chapter 6 sought to review two modified diagnostic tools used in other settings for the diagnosis of paediatric TB and one new algorithm provided by the WHO. Confirmation of diagnoses can be achieved by nucleic acid amplification testing or culture, however, there is an absence of a globally available gold standard for clinically diagnosed cases. It is therefore possible that validity of our findings in Chapter 6 are not reproduceable in other settings as the gold standard method used as a comparator and point of diagnostic reference against modified diagnostic tools were based on diagnostic decisions from two experienced TB physicians. One of the recommendations resulting from our findings include the development and validation of a paediatric diagnostic tool that is appropriate in this setting.

7.3.4 Data limitations

Many of the data limitations have been previously described in Chapter 2. Notably, as a result of changes to the classification of ‘probable’ cases by the Queensland Communicable Diseases Branch in 2018, to either ‘probable’ or ‘unsure’ and the confusion in the Torres and Cape TB Control Unit around data requirements as a result of this change, it is possible that some

clinically diagnosed cases diagnosed in the study population are not available in the Notifiable Conditions System. This did not impact any study within this thesis as Chapters 3 and 4 only included laboratory confirmed cases, and Chapters 5 and 6 included presumptive, laboratory-confirmed, clinically diagnosed and previously diagnosed cases in analyses.

While eight methods were used to collect and collate data on patients in this thesis, and I had Ethics approval to access data within the Cairns TB Control Unit, I was unable to obtain site specific application clearance from the data custodian. Regardless, I am confident that the findings within studies this thesis were not impacted as historic data was available from other included sources.

7.4 Strengths

There was value in having fit for purpose research done by a clinician working at the coal-face of TB management at the Torres Strait / PNG international border. Advantages of being in the dual position as both researcher and clinician included having access and know-how to obtain very detailed data.[2] As an example, researchers who do not work in the field as clinicians may not be aware that there can be substantial amounts of information found on pathology and imaging request forms, that may not be found to the same degree of detail in a patient's medical record. Being a researcher living in the field enabled me to drill down on individual patient data instead of accessing bulk queries run by those external to the research team. Awareness of the finer data points I had access to in my professional life, meant that formulated research questions would be answerable. Having local clinical knowledge also enabled the development of comprehensive datasets through data linkage from multiple different sources.

Another advantage was the ability to read and interpret the social constructs of a particular location as these subtleties may be missed by researchers not embedded in the social fabric of living in the same community being studied.[2] An example of this was understanding local perceptions of real or perceived threats of cross-border TB transmission based on real-time patient/clinician interactions and connections over time, rather than by taking educated guesses based on the literature from other contexts. Having an in-depth understanding of context not only assisted with data analyses and the interpretation of research findings, but it will continue to assist in my clinical role as I now work to translate evidence into practice.

7.5 Discussion

Although the order of chapters within this thesis do not follow the standard clinical pathway from recognition of signs and symptoms of TB to specimen collection/diagnosis/diagnostics through to commencement of effective treatment and outcome, each component of the standard clinical pathway will be used in this chapter to integrate discussion points and the implications of new findings within this thesis. Further, the implications of the research can be broadly categorised into practice, education, leadership, policy and research. The findings in this thesis are consistent and supported by WHO's End TB Strategy.[1] Initiatives have been implemented in the Torres and Cape Tuberculosis Control Unit as a result of evidence derived from this research, and this discussion will describe changes in policy and practice that are aimed at providing and enacting lasting change.

7.5.1 Recognition of the signs and symptoms of TB

7.5.1.1 WHO End TB Strategy

Pillar 1. Integrated, patient centred care and prevention.

O what can ail thee, knight-at-arms,
Alone and palely loitering?
The sedge has withered from the lake,
And no birds sing.

O what can ail thee, knight-at-arms,
So haggard and so woe-begone?
The squirrel's granary is full,
And the harvest's done.

I see a lily on thy brow,
With anguish moist and fever-dew,
And on thy cheeks a fading rose
Fast withereth too.

- Poem 'La Belle Dame sans Merci', in which the author John Keats was seemingly aware that the symptoms of tuberculosis would take his life

TB is endemic in the Western Province of PNG that borders the Australian Torres Strait Islands, and studies in this thesis have demonstrated that the epidemiology of TB in the Torres Strait / PNG border region has changed over time. This thesis has demonstrated the need for increased awareness of both clinicians and community members about the signs and symptoms of TB, as evidenced by a rise in case numbers, distribution and transmission of drug-resistant TB (DR-TB) over the international border (Chapter 4.1); high rates of acid-fast bacilli (AFB) positive cases, particularly adults from PNG with cavitary disease which indicates advanced disease (Chapter 3); the diagnosis of nearly one in three children indicating community transmission from the adult population; potential underdiagnosis of extrapulmonary (EP)-TB and the impact of malnutrition on the paediatric population (Chapter 6).

At first glance, the wide dispersion of cases and the identification of DR-TB 'hot-spots' shown in Chapter 4.1, may indicate that patients who had commenced on treatment for TB were non-compliant. Failure to complete treatment or inadequate treatment may lead to complications and drug-resistance.[3] However, the rise and distribution of DR-TB in the Treaty and non-Treaty villages shown in Chapter 4 is reminiscent of serious health system deficits, in which primary health mechanisms were not available in most villages and may have contributed to patients with presumptive TB going unnoticed. However, it is also likely that there may have been other sociocultural, ethnographic, and geopolitical factors at play.

Equitable 'Health for All' was a goal agreed on by 134 member nations of the WHO, who signed The Alma-Ata declaration in 1978, declaring that Primary Health Care was a human right.[4] However, financing aid posts and basic medical units which provide PNG villagers with access to primary health care and Health Workers as the crucial link between community and the health system, was hampered by debt reduction and repayment of loans issued by the World Bank, which resulted in decreased funding for health.[4] Re-prioritisation of funding for health is a recurrent theme in PNG, and in 2018, Daru General Hospital temporarily closed when funds allocated to health care were redirected by the PNG Government to pay for the Asia-Pacific Economic Cooperation (APEC) summit in Port Moresby. This may partially help to explain the peak in PNG nationals diagnosed with DR-TB in the Torres Strait (Chapter 4.1) as residents had limited healthcare options during this time.

Indicators of successful TB control strategies used in other settings are most commonly measured by reductions in mortality and morbidity[5] however retention in care from symptom onset and recognition, to diagnosis and time to effective treatment commencement and outcome

data may be more meaningful measurements in the Torres Strait / PNG cross-border setting. This is because most patients are referred back to the PNG health system for ongoing care, and this coupled with restrictions of movement associated with the inability to recall patients across the border means that loss to follow up across the border is a reality for many. In Chapter 4.3, I identified a reduction in time to effective treatment over programmatic year groups, and it is possible that mass community TB education improved outcomes for patients diagnosed between 2014-2020 (Chapter 4.4). Retention in care starts with symptom recognition and the path to treatment is dependent on the recognition of signs and symptoms experienced by patients and assessed by clinicians.[6]

Recognising the signs and symptoms of PTB is usually straightforward in adolescents and adults. To help guide primary health clinicians, a systematic approach supported by explicit procedures were implemented in the Torres Strait in 2016. However, clinicians coming to work in the region may have little awareness of TB epidemiology in Australia and/or little or no previous experience with diagnosing TB. Although the Cross Border TB procedure and supplementary documents (Appendices J2 – J5 and J11)[7-11] and the TB procedures relevant to residents of the Torres Strait Islands (Appendices J9 and J10)[12-13] are available in all PHCs and on the workplace intranet in the Torres Strait, adherence is reliant on the Health Centre Manager's support and the TB Unit's commitment to onboarding education for new staff and refresher education for existing staff.

Despite the risk of exposure to AFB positive TB cases for clinicians posted to the Top Western Cluster in the Torres Strait (Saibai, Boigu, Dauan), the only mandatory training which applied to TB pre-COVID-19 was mask fit-checking, which has been upgraded to mask fit-testing since the pandemic. Chapter 4.1 demonstrated that the risk of DR-TB transmission into Saibai Island has increased in recent times. This lack of training is compounded by the high turnover of staff, however, since 2017, clinicians working on Saibai Island have received education on symptom assessment and local TB procedures, courtesy of the TB Unit's Indigenous Health Worker. Despite this, the evidence in this thesis supports the need for continued training of clinicians and new and innovative solutions to support patients in need of safe and rapid TB care. Future qualitative research that focuses on clinician confidence in recognising and diagnosing TB and identifying what staff think may increase their confidence would be helpful. Early recognition by health staff of symptoms of TB enables early intervention and this is particularly important for patients who are infectious with AFB positive TB.

In Chapter 3, a higher rate of AFB positivity was observed in PNG nationals than in residents of the Torres Strait. This could possibly indicate that residents of the Torres Strait Islands are more inclined to access health care at the early onset of symptoms due to ease of access, whereas PNG nationals - who experience greater costs and challenges when accessing health care - may be more likely to present to health facilities only when their symptoms worsen or do not resolve. AFB positive patients are twice as infectious as AFB negative patients.[14] As has been demonstrated throughout this thesis, human immunodeficiency virus (HIV) does not appear to be a driver of high case notification rates in the Torres Strait / PNG border region, however AFB positivity in addition to cavitary disease and HIV negative status has been found to be associated with increased risk of infectiousness in other settings.[14] It is more likely, however, that the rapid rise in case notifications over time were due to extensive treatment delay.

The national average rate of bacteriologically confirmed AFB-positive sputum smears in Australian TB programs is 50%,[15] however Chapter 3 identified 70% of PTB cases with at least one positive sputum smear. AFB positive patients have a higher burden of disease and poorer prognosis.[16] Late presentation with symptomatic AFB positive disease is associated with an increased infectiousness and transmission risk.[17] Chapter 4.3 identified that the median time from onset of symptoms to effective treatment commencement in the region was 124 days, with a significant improvement in recent years to 29 days. However patients with a treatment delay >28 days are more likely to be highly infectious[14] so there is still room for improvement.

Chapter 4.4 showed AFB positivity in patients with combined PTB and extrapulmonary (EPTB) and found that just under half of all DR-TB cases (45%) had extrapulmonary involvement. In Chapter 6, it was demonstrated that the 2016 symptom recognition procedure and supplementary documents used in the Torres Strait included assessing children for enlarged lymph nodes, but lacked clinical parameters or guidance that would support clinicians in recognising and collecting specimens to assist in the diagnosis of other forms of EPTB.

Chapter 5.2 demonstrated a higher proportion of death in presumptive TB patients that did not meet aeromedical evacuation criteria compared to the proportion that did meet aeromedical retrieval criteria and died. This indicates that current early warning tools used in the Torres Strait to detect clinical deterioration in patients presenting with presumptive TB are not prescriptive enough to be used for TB patients. Chapter 5.2 also demonstrated that a high proportion of children with presumptive TB met criteria for severe malnutrition, and although the ramifications for malnutrition and TB in children discussed in Chapter 5.2 are severe, the

current TB screening tool used in the Torres Strait does not collect age/weight percentile data that could have an impact on clinical and aeromedical retrieval decisions. The TB screening tool used at the time of the research (Appendix J3)[8] required a response to one question about unexplained weight loss and the current weight of the patient, but there is discordance between the TB screening tool and the early warning tool as one does not inform the other. Further, chapter 6 identifies a significant gap in diagnostic capabilities to support paediatric TB diagnoses.

Thus, there are three main gaps in current healthcare delivery for patients with presumptive TB.

- Firstly, to enhance detection of TB in both adults and children, mechanisms within policy, clinical tools and training are required to assist in the recognition of EPTB symptoms.
- Secondly, early warning tools that are specific to the nuances of presumptive TB which complement mainstream early warning tools, and that allocate points to malnutrition risk and are accepted for use by Rural Generalist Practitioners are required.
- Thirdly, a TB screening tool that is fit-for-purpose to detect malnutrition risk in paediatric patients with presumptive TB is required. Baseline measurements that are simple to collect in remote settings should be considered for inclusion such as middle upper arm circumference, height for body mass index, and age/weight percentiles that can be systematically calculated within existing patient information software.

In the Torres Strait / PNG border region, screening patients with presumptive TB is a balance between the potential health benefit for individuals, and the prevention of cross-border TB transmission risk. Passive TB case detection in Australia relies on symptomatic individuals presenting to a health facility for testing. Screening processes used at the border were described in Chapter 1, and while screening does occur in symptomatic patients, which would constitute passive case detection, our target population is considered high-risk and a heightened index of suspicion is warranted. Under the passive case finding paradigm, there are commonalities – identifying cough, fever, weight loss, night sweats and haemoptysis, and although we know that these symptoms could represent a number of health conditions, we have demonstrated that future approaches to TB screening need to reflect new knowledge identified in this thesis that illustrates the epidemiological profile in the region. Symptoms of TB are the same, irrespective of nationality or location of residence.

7.5.1.2 WHO End TB Strategy

Pillar 2. Bold policies and supportive systems

In terms of screening patients, there are three main findings in this thesis that indicate that prompt review of policies, procedures and clinical practice is required.

1. Chapter 6 identified that additional questions need to be added to existing TB screening tools to help clinicians recognise additional sites of EPTB.
2. Chapter 6 identified that there are deficits in the way that paediatric TB is identified and that development of a region-specific paediatric diagnostic tool or algorithm for presumptive TB paediatric patients is required.
3. Chapter 5.2 identified that generic deterioration detection scores used in Queensland do not identify the most serious of TB case presentations, and that a scoring tool that is specific to TB patients is required for use in the Torres Strait.

Chapter 5.2 demonstrated that local policies and procedures designed to support equitable healthcare were inconsistently applied. Therefore, it may be necessary for both countries to establish legal frameworks to ensure that the right to health care and continuity of care is available, respected, and achievable for all patients presenting with presumptive TB.[18]

7.5.2 Specimen collection / diagnosis / diagnostics

7.5.2.1 WHO End TB Strategy

Pillar 1. Integrated, patient centred care and prevention.

> TB or not TB, that is the question.
>
> The most commonly used mock quote from William Shakespeare's Hamlet within TB-related journal articles globally.

The benefit of collecting adequate specimens for the diagnosis of TB is three-fold: 1) confirmation of disease enhances TB detection; 2) identification of drug-resistance may occur and 3) it supports rapid commencement of effective treatment. This is particularly important in settings with high rates of PTB and the focus of need is demonstrated in Chapter 4.4 where 92% of DR-TB cases diagnosed had pulmonary involvement. Chapter 3 identified that the collection of two sputum specimens had adequate diagnostic yield to identify the majority of PTB in the region. This is consistent with other studies with access to comparable laboratory capabilities.

In an Italian study of 359 samples subjected to *Mycobacterium tuberculosis* complex testing, 92% of patients were diagnosed with PTB from the first two samples.[19] Similarly, in an American study of 120 patients with culture-confirmed PTB in Minnesota, 95% of cases were diagnosed from the first two sputum specimens.[20] Although 96% of smear positive cases detected in our study were from one or both of the first two samples collected, our setting differs significantly from other TB programmes with access to well-resourced laboratories.

Although Chapter 3 demonstrated high diagnostic yield, success relies on adequate specimen collection and proper packaging and transportation in remote settings.[21] Diagnostic yield studies typically exclude very young children from study cohorts due to the difficulty in collecting adequate specimens for the diagnosis of PTB and limited sensitivity of microbiological testing in children.[22] In contrast, we demonstrated good diagnostic yield in children in Chapter 3, with 93% of children being diagnosed within the first two specimens, regardless of the quality of the specimens provided. An unexpected finding was that children in our study were proficient in voluntary expectoration. Although we do not fully understand the reasons for this, we can hypothesize that delayed presentation may have led to advanced disease and damage to the lungs. The PNG Treaty village population relies on wood for cooking and burnt wood generates irritant gases that with sustained exposure, may aid in voluntary expectoration.[23] Alternative methods of specimen collection that don't rely on sputum, such as oral tongue swabs, could potentially further enhance the diagnostic capacity for detecting TB in individuals who are unable to produce sputum.

The paediatric TB burden in PNG has been reported to be 26%.[24] In contrast, Chapter 5 showed a higher-than-expected proportion (37%) of TB cases diagnosed in PNG nationals presenting at PHCs in the Torres Strait Protected Zone (TSPZ) under the age of 18 years, and it is likely that due to limited access to health services and difficulty securing a diagnosis in children based on symptom recognition and risk factors (Chapter 6), that these numbers are significantly higher. Chapter 1.2 identified poor nutrition as a theme in the scoping review and Chapter 6 identified that over half of all children who presented to a PHC with presumptive TB were under the third percentile for age and weight or with severe malnutrition. This finding, combined with the high AFB positivity rate reported in Chapter 3, demonstrates that adult to child transmission is occurring in the region and thus, efforts to increase the diagnostic yield are warranted.

Notwithstanding some promising results, we were able to demonstrate that the diagnostic yield for all age groups may be further improved. In the Torres Strait / PNG border region where DR-TB is a growing threat, we have a responsibility to increase our efforts to obtain quality specimens. In remote settings, nasopharyngeal aspiration in children is a simple outpatient procedure as is sputum induction using hypertonic saline in adults. In in-patient hospital settings, nasogastric aspiration has proved to be an effective alternative to voluntary expectoration in young children.[25] With appropriate training, these are techniques that can be easily implemented in the Torres Strait, and diagnostics expedited with the right technology in the right place.

We have hypothesised that a reduction in time to treat delays could be achieved by the establishment of advanced diagnostic technology located in the Torres Strait. Chapter 3 identified a high proportion of smear negative PTB cases whereby culture confirmation takes six weeks. When Xpert MTB/RIF Assay (Xpert) was implemented in November 2010 in Brisbane (>2,000 kilometres away from the point of collection) for all samples collected in the Torres Strait, a reduction in time to treat was observed in DR-TB patients including those with smear negative disease. In Chapter 4.3 it is acknowledged that although the difference between the time to effective treatment commencement pre and post-Xpert was not statistically significant, this was likely due to the small size of the study population. It is possible that if the study was not limited to DR-TB cases only, then a significant difference in the time from onset of symptoms to effective treatment commencement would have been observed.

Use of effective diagnostic tools in remote areas has become an important public health focus to halt TB transmission and promote rapid diagnosis and subsequent effective treatment commencement.[26] With the COVID-19 pandemic, access to Xpert has increased as it has been used as the primary tool for rapid point of care testing in the Torres Strait. As TB will no doubt continue to reign supreme long after the COVID-19 pandemic, limited funds to access advanced diagnostic tools should no longer be a reason to delay implementation of Xpert in the Torres Strait in the future.

7.5.2.2 WHO End TB Strategy

Pillar 2. Bold policies and supportive systems

The Torres and Cape Hospital and Health Service (TCHHS) has a responsibility in the Torres Strait to also ensure that patients presenting to outer island clinics are immediately identified as

at-risk for unfavourable outcomes or life-threatening situations that require advanced medical interventions or additional specimen collection or measurements. In terms of enhancing surveillance and protecting those most-at-risk, there are four main lines of enquiry in this thesis that indicate that prompt review of local policies, procedures and clinical practice is required.

1. Chapter 4.4 identified that low lymphocyte levels were significantly associated with unfavourable outcomes in patients indicating an ongoing review of blood test results (lymphocyte, albumin and haemoglobin) in patients with both presumptive and active TB is warranted.
2. Chapter 5.2 identified severe malnutrition in the paediatric population and Chapter 6 identified that collection of additional data (middle upper arm circumference and body mass index) may help to improve paediatric patient identification/diagnosis and outcomes.
3. Chapter 6 identified a high proportion of paediatric patients with lymph TB and that the use of fine needle aspiration may help to increase diagnostic yield.

7.5.3 Treatment and Outcome

7.5.3.1 WHO End TB Strategy

Pillar 1. Integrated, patient centred care and prevention.

> When we take a place-based approach to governance and service delivery, we are better able to understand the complex intersections between policy arenas: the relationships between disparate sectors and disciplines can be traced as their complex intersections weave through this place.
>
> - Mark Moran and Jodie Curth-Bibb, Too Close to Ignore: Australia's Borderland with PNG and Indonesia[27]

Predicting which patients will have unfavourable outcomes may assist programs to determine where resources are best focused. As traditional inhabitants of PNG are not required to undergo TB screening as they cross the Australia / PNG border, there remains a risk of TB transmission to residents of the Torres Strait. To prevent transmission from border communities to other Torres Strait Islands and mainland Australia, there are public health imperatives to use new evidence to augment existing practice in the pursuit of better management of TB patients.

Understanding the epidemiology behind unfavourable outcomes for patients with both new and previously treated DR-TB was a focus in Chapter 4 and will help an evidence-based public health response in this region. In Chapter 4.4 an association between low lymphocyte levels and unfavourable outcomes in patients diagnosed with DR-TB was identified. To achieve optimal outcomes, diagnostics need to go beyond specimen collection for mycobacterial culture. Various biomarkers such as haemoglobin, albumin and lymphocyte levels have been used to predict severity of disease, immunodeficiency and decreased survival in TB patients.[28] While we did not find a significant association between low haemoglobin and low albumin levels and unfavourable outcomes in DR-TB patients this was likely due to insufficient power as the proportion of patients with anaemia and low albumin was high.

TB influences and interacts with immunological and haematological factors. The timing of blood collection and values measured during the treatment or disease progression can introduce confounding or bias. This is because measurements are likely to change and fluctuate throughout the course of the disease or treatment. Basing conclusions on a singular snapshot of data and drawing inferences demands a careful and considered approach. Unfavourable outcomes for DR-TB patients diagnosed in the Torres Strait / PNG border region may therefore be impacted by vulnerabilities created by high rates of other communicable and non-communicable conditions.

One of the most significant findings reported in Chapter 4.4 was the high proportion of unfavourable outcomes in patients with comorbidities/coinfection. Renal impairment, diabetes and HIV can each impact immune responses, and immune abnormalities that suppress the host immune response may be associated with unfavourable outcomes in patients with DR-TB.[29] Although the case numbers were small, all patients with TB/diabetes died in Chapter 4.4. It is widely reported that Indigenous Australians experience higher rates of chronic conditions such as diabetes and renal disease and while the prevalence of type 2 diabetes in PNG is unknown, [30] the prevalence of type 2 diabetes in residents of the Torres Strait Islands is reported to be the highest in Australia.[31] Given the closeness and lifestyles between populations on both sides of the border it is not unreasonable to expect PNG nationals being similarly affected by type 2 diabetes and this should be taken into consideration when they present with presumptive TB.

The United Nations Millennium Development Goals (2005-2015), backed by the WHO, supported vertical programs to achieve cure and prevention of TB disease,[4] however, in the lead up to publication of the WHO End TB Strategy in 2014,[1] TB experts contributed to a shift in

the global policy mindset away from vertical programs and towards integrated and patient-centred collaboration to manage patients with TB and comorbidities.[32-34] This thesis identified a critical need for collaboration with other sub-specialties as health services in the Torres Strait operate within vertical program models of health care delivery.

In the Torres Strait, the organisational structure of the TB Unit and the physical location of diabetes, renal and sexual health services are completely separate entities. In Far North Queensland, TB Units do not sit under Public Health teams, and despite the severe consequences of TB/HIV coinfection and the rapid advancement from latent to active disease, access to local HIV patient data, is strictly prohibited outside of sexual health services. Collaboration between the Torres and Cape TB Unit and other sub-specialities is still in its infancy. While HIV patients are screened for exposure to TB using QuantiFERON Gold Assays, local TB clinicians are not involved in the management of this, are not notified if HIV patients develop signs and symptoms of TB and have no insight into whether sexual health clinicians are trained in recognising presumptive TB in HIV patients. Therefore, increased collaboration between these sub-specialties is warranted, and patient-centred benefits to having a multidisciplinary approach ensure that neither the disease is overlooked.[35]

Patients with TB are not screened for diabetes or renal impairment, and patients diagnosed with diabetes or renal impairment are not consistently screened for TB across the TCHHS region of responsibility. In immune compromised patients in high-risk settings, testing for and treating Latent TB may help to reduce the likelihood of progression to active TB disease.[36,37] Once disease progression has occurred in immunocompromised patients, a higher bacterial load has been reported in patients with AFB positivity, leading to extended sputum conversion times and prolonged treatment.[3] Creating partnerships in other sub-speciality areas and with Indigenous Health Worker support may extend the scope and reach of TB recognition, reduce diagnostic delay, enable patient-centred care and result in improved outcomes.[1]

In studies conducted prior to the availability of TB drugs, approximately 70% of patients with AFB positive TB died, and approximately 20% of patients with AFB negative / culture-positive PTB died within 10 years of diagnosis.[38] If TB cases are not found and treated, the more likely outcome is death, and multiple chapters within this thesis identified subsets of the at-risk population that warrant increased focus. In Chapter 4.3, new cases were significantly associated with reduced treatment delay, indicating that initiatives are required to find and treat previously treated cases. Globally in 2019, 17.7% of previously treated cases and 3.3% of new cases were

diagnosed with rifampicin resistant MDR-TB.[39] In contrast, 26% of MDR-TB patients in Chapter 4.3 had previously received treatment, nearly one in five DR-TB patients had received previous treatment (Chapter 4.4) and new cases were nearly four times as likely to have rifampicin resistance (Chapter 4.1). These statistics suggest that previously treated patients are fuelling much of the TB epidemic through relapse, and identification of predictors of treatment default may aid in reducing the infectious pool and transmission risk.[40]

In Chapter 4.1, females were found to be more than twice as likely to be diagnosed with MDR-TB however, there was no effect of sex on treatment delay for patients with DR-TB in Chapter 4.3. In Chapter 4.4, being a close contact of a known TB case reduced the likelihood of DR-TB patients having an unfavourable outcome, however a study conducted on Daru Island[41] reported longer treatment commencement delays in symptomatic household contacts of MDR-TB cases when compared with drug-susceptible TB (DS-TB) cases. As treatment delay invariably leads to unfavourable outcomes, the findings in this thesis are therefore in contrast with the TB Programme on Daru despite sharing patients from the same region. However, none of the variables assessed in both Chapter 4.3 and the Daru study were highly predictive of unfavourable outcomes and these results coupled with the findings from Chapter 4.1 where neighbouring villages had very different rates of DR-TB diagnoses suggests that there may be local factors at play which warrants further research. The evidence also demonstrates the difficulty in determining which patients are most at-risk of experiencing lengthy delays and unfavourable outcomes, but emphasises the importance of increased attention to symptom recognition and early screening.

It is well understood that adverse drug reactions may lead to treatment interruption and poor prognosis.[42] However, there are many other factors that likely contributed to past treatment default and failure, including past global and local policy failures. In 1995, the WHO determined that treatment for MDR-TB was not suitable in poor countries as the cost to treat was considered an expensive luxury.[43] The official WHO policy was that MDR-TB treatment should only commence in developing countries once a fully functioning and successful Directly Observed Therapy (DOT) Shortcourse program was available for DS-TB patients.[43] Official policy later changed in 2002 to recommend DS-TB treatment regimens in populations with <10% DR-TB case load.[44] Like many other TB programs at the time, Daru did not realise that MDR-TB affected their population owing to the absence of epidemiological data. At the time, medications used to treat DS-TB were not consistently available in the Treaty villages and as

DR-TB development is almost always the result of medical or public health deficiencies,[44] there was little salvation for patients presenting to Daru General Hospital who had failed to improve on treatment. Acknowledgment of the DR-TB situation wouldn't come until 6 years later in 2008 when Queensland Health TB physicians sounded the alarm about cross-border MDR-TB.[45]

7.5.4 Policy and Practice

7.5.4.1 WHO End TB Strategy

Pillar 2. Bold policies and supportive systems

> In an almost forgotten historic event, in a place called Alma-Ata, the governments of the world came together to make a revolutionary promise. Full health care would be extended to all, beginning with the poorest on earth.
> But this grand vision never came to be. Instead, larger forces from wealthier countries created plans that crippled the once-rising nations. They ushered in poverty, disease, and chaos.
>
> - Ophelia Dahl, co-Founder of Partners in Health –
> in Documentary: "Bending the Arc"[43]

7.5.4.2 Policy implications within the thesis works

Chapter 3 explored the value of diagnostic yield of sputum specimens under the lens of a historical policy decision that in countries with well-functioning laboratory support, the collection of three specimens were required for the diagnosis of PTB. While well-functioning laboratory support is available in the state of Queensland, it is over 2000 kilometres away from the furthest point of collection, and policy decisions to collect three specimens did not factor in constraints of distance, remoteness and humidity.

The number of specimens collected from PNG nationals who presented to health facilities in the TSPZ varied over time. Up until 2015, the number of specimens collected from PNG nationals was in-part related to the length of time the patient spent on-island in the Torres Strait. There was a degree of freedom during that time, in which PNG nationals had greater flexibility to present to Australian PHCs over three consecutive days to provide sputum specimens. As the highest risk of transmission of PTB occurs prior to diagnosis and treatment, and as sputum smear-positive PTB is of public health significance and should be a priority for TB control units,[46] Indigenous leaders in the Torres Strait expressed concern about potentially infectious

TB patients from PNG remaining untreated in the local community in the Torres Strait and requested a review of Queensland Health processes.

Community consultation and participation from cultural leaders in the Torres Strait during the TB policy formulation in the lead up to the Torres and Cape TB Control Unit establishment in 2016, were and still are considered an important component of eradicating TB in the Torres Strait. The outcome from consultation with local leaders, and members of the Clinical Collaborative Group was that PNG nationals with presumptive PTB would be prohibited from remaining on island after presenting to PHCs in the TSPZ, and would be referred back to the PNG health system if aeromedical evacuation was not required. With a view to ensuring the best diagnostic outcomes possible for patients, further consultation with the Queensland TB Expert Advisory Group led to agreement that two on-the-spot sputum specimens could be collected from PNG nationals presenting with signs and symptoms of TB to PHCs in the TSPZ. From a programmatic perspective, it was therefore important to ascertain the feasibility of collecting two specimens for the diagnosis of PTB, determine any gaps in service delivery and identify initiatives that could improve diagnostic yield in the region.

A key finding of this research was the disconnect between the clinical issue of TB and the policies and procedures created to guide clinicians, the uptake and adherence to policy, and political support. Cross-border policies and procedures used in the Torres Strait exist to protect the human rights and health of patients and provide clinicians with practical means to provide healthcare in this region. Chapter 5.2 demonstrated the impact of clinical decisions in relation to local policy, the disconnect between policy and practice, a lack of governance at the highest levels and the effect this has had on patients' lives. Studies find that clinicians disconnected from their patients have reduced empathy,[47,48] and one explanation for the inconsistent decision-making observed regarding PNG nationals is the vast geographical and cultural distances across the Torres Strait which may diminish clinicians' sense of empathy and justice. There is a notion that PNG nationals seeking healthcare in the Torres Strait are 'liminal' constituents, stuck in a no-man's land in the shadows of an 'Australians-first' remit where patient needs frequently surpass available resources.[49]

Quality and safety of patient care relies on effective communication between attending clinicians.[50,51] However, miscommunication between clinicians can occur and the efficiency of systems can be impacted by power imbalances between physician and nurses and between senior and junior physicians where the fallout may be reluctance to comply with policy or

provide strong advocacy for deteriorating patients.[51,52] Miscommunication between doctors and nurses as a result of divergent training styles has also been documented[53] and can lead to errors, flawed medical assessments and delays in diagnosis and treatment.[50]

Policy can be a driver of change but requires adequate governance and commitment. In recent times, we have witnessed the havoc that the COVID-19 pandemic has unleashed on the world, and the mobility and redirection of collective resources across international borders to address it. This was also evidenced in academia as publishers gave priority to COVID-19 related papers, perhaps neglecting other key communicable diseases. Although the Australia / PNG border was largely closed during the pandemic, initiatives implemented to improve the management of TB in the region did not cease. Should other pandemic events occur, it will be important for the TCHHS to plan for TB management in the region so as not to lose momentum.

Organisational and policy arrangements within the Torres Strait that embrace, in principle, the sharing of epidemiological data and promote a collective clinical front is evidenced by Queensland Health's response to COVID-19. As TB will remain an issue long after the current pandemic, we can only hope for the same integrated approach. As there is an ethical/moral responsibility to act upon research generated by clinicians at the coal-face, it is the responsibility for clinician-researchers to ensure translation occurs, including advocacy if applicable.[54] This ensures that research outputs are not just an exercise in academic endeavour.

7.5.5 Translational Activities Deriving Directly from this Research

7.5.5.1 WHO End TB Strategy

Pillar 3. Intensified research and innovation

The findings presented in this thesis have led to a number of changes in the management of TB in the region and have provided an evidence-based foundation to inform the development of new clinical tools and pathways to reduce the impact of TB on residents of the Torres Strait Islands and the coastal villages of PNG that access health services in the Torres Strait. The findings from this work are informing the development of multiple changes to clinical practice, policies and procedures in the region. It is important to note that this thesis was commenced in 2016 which was the same year that the Torres and Cape TB Control Unit was established.

Chapter 1 – Scoping and narrative reviews

Multiple initiatives that were described as potentially impacting the results in Chapters 4.3 and 4.4 were implemented by the Torres and Cape TB Control Unit as a result of the findings in both the scoping and narrative reviews in Chapter 1. Chapter 1 identified programmatic risks and gaps in the management of TB in the Torres Strait / PNG border region, and highlighted opportunities for local improvements based on the experiences of TB control efforts in other challenging situations. To enable enhanced surveillance at the border, all TB screening materials were translated into Tok Pisin, a phonetic language spoken by PNG nationals residing in many of the Treaty villages. This has allowed PHC clinicians to better communicate with patients who may have been previously unable to articulate in English their signs and symptoms and risk factors for TB. Further, linguistically and culturally appropriate TB education materials have been provided to PHCs in the Torres Strait and specific TB-related onboarding information packages are available to all staff.

Chapter 1 identified the strengths and benefit of providing DOT for patients. From 2016, the Torres and Cape TB Control Unit have been coordinating and training PHC clinicians in the principles of providing DOT. Upon a positive diagnosis, a nurse from the Torres and Cape TB Control Unit will now travel to the PHC where the patient will be receiving DOT and provide all staff with appropriate patient-centred training and regular support meetings. It was during 2016, that the Torres and Cape TB Control Unit obtained permission to train Indigenous Health Workers in DOT, a task previously allocated to Registered Nurses. Two additional initiatives were implemented to assist patients achieve treatment completion and enable some level of food security. In 2019, DOT via telehealth was commenced for residents of the Torres Strait and the Torres and Cape TB Control Unit entered into a partnership with Island Board of Industry Service grocery stores and introduced food voucher incentives provided to patients at the end of each week of completed treatment.

Chapter 4.4 identified that prior to 2016, a higher proportion of patients had an unknown outcome and Chapter 4.3 identified excessive treatment delays prior to the establishment of the Torres and Cape TB Control Unit in 2016. There was evidence in the literature reviewed for Chapter 1, of many examples of successful cross-cultural collaboration in TB programs, however within the grey literature, there was some evidence of disconnect between the Cairns TB Control Unit and the TB programme at Daru General Hospital. To enhance cross-border collaboration and strive for safer patient outcomes, the Torres and Cape TB Control Unit

established early communications with the TB programme at Daru General Hospital. With support from a former TCHHS Chief Executive, and in collaboration with the TB physicians in the Torres and Cape TB Control Unit, visits to Daru General Hospital were arranged to establish shared data requirements and operational protocols. The benefit of respectful cross-border collegial relationships is evidence by jointly developed cross-border policy documents[7,55,56] and improvements in patient outcomes and effective time to treatment commencement described in Chapters 4.4 and 4.3.

Of note, with the COVID-19 pandemic, there were significant structural changes to the PNG health system in the Western Province, including staffing changes within the Daru TB Programme and the temporary cessation of the Health Issues Committee meetings. Priority was given to COVID-19 efforts globally, at the detriment of other key global health issues and this impacted the relationships and commitment to shared data agreements between the Torres and Cape TB Control Unit and the TB programme on Daru. It is now written into the National Partnership Agreement (NPA) that some funding be allocated to facilitate the exchange of information between the Torres and Cape TB Control Unit and the TB program at Daru General Hospital. [57]

Chapter 2 – Data Collection

As a result of the cross-border TB data integrity project, described in Chapter 2, it is now a requirement for all patient files of PNG nationals to be uploaded into a secure electronic medical record. Best Practice software is the designated repository for all occasions of service of both residents of the Torres Strait Islands and PNG nationals attending health services in the Torres Strait. Future researchers will therefore now have access to a consolidated source of information pertaining to TB and other conditions of public health significance in PNG national patients in the region.

Chapter 3 – Diagnostic Yield

Chapter 3 demonstrated very high diagnostic yield using two sputum specimens. Although the TCHHS were already collecting two specimens at the border for PNG patients with presumptive TB, these results provided the evidence that was needed to instil a moral and ethical-based calmness within the clinical team and demonstrate that staff were adhering to the principles of doing no harm within the constraints of the ‘no-recall’ of PNG patients policy for repeat specimen collection.

'The Lady doth test too much' paper was shared with the Torres and Cape TB Control Unit as well as with the TCHHS Director of Patient Safety and Quality and the Executive Director Medical Services. Further consultation occurred with the Queensland Expert TB Advisory Group, and the Torres and Cape TB Control Unit were given permission to discharge patients after they have received two negative sputum specimens. This applies to residents of the Torres Strait Islands and Cape York communities and affects both inpatients in hospital and outpatients placed in isolation. This has led to cost savings in terms of length of hospital bed stay and has had a direct impact on individuals who may return to work and their everyday activities earlier than previously permitted. However, a third specimen is collected if a patient is strongly suspected of having PTB.

As a result of the findings in Chapter 3 which demonstrated the need for additional clinician training, the Torres and Cape TB Control Unit formulated, with full consultation with clinical and pathology staff, a new sputum induction procedure for use in the TCHHS. This included a commitment to hospital-based staff on Thursday Island that TB nurses would provide face-to-face training as required. To support uptake of this new clinical procedure, TB nurses have also provided training in sputum induction to clinicians working in high-risk PHCs in the TSPZ.

Prior to presenting to Saibai Island PHC, PNG nationals with presumptive TB often stay with family members on Saibai Island while symptomatic. In recognition of the high proportion of smear positive PTB identified in Chapter 3 and the benefits of community involvement in TB prevention in Chapter 1, the Torres and Cape TB Control Unit partnered with Tagai School on Saibai Island and introduced annual TB education sessions for students in year five (10-11 years of age). It is our hope that students partaking in fun educational activities in school about TB will take the messages home and that by normalising TB education in the primary curriculum, we can start to break down some of the stigma associated with TB and Saibai Island.

Although Chapter 3 identified minimal errors in packaging specimens and arranging air and sea transportation, there were some specimens that were not tested as they exploded in transit, were too old or were not registered properly and hence, there was room for improvement. Consequently, as the Nursing Director of the Torres and Cape TB Control Unit, I met with both the Pathology Queensland Chief Scientist on Thursday Island and liaised with the Queensland Mycobacterium Reference Laboratory in Brisbane. Prior to this study, discarding of specimens was at the discretion of Pathology Queensland if they did not meet labelling or minimum quantity requirements. As there is no opportunity to recall patients to collect additional

specimens, it was agreed that the Queensland Mycobacterium Reference Laboratory would accept all specimens irrespective of quality, that were collected from PNG nationals attending health services in the TSPZ. Further, the Torres and Cape TB Control Unit assumed responsibility for all specimens collected in the Torres Strait Islands and became the direct point of contact for Pathology Queensland on Thursday Island if poor labelling meant the specimen was at risk for a 'no-test' or if the specimen leaked in transit.

After the diagnostic yield study was complete, I investigated learning opportunities for safe specimen packaging. Although not listed on the TCHHS mandatory training matrix, I discovered that it is a mandatory requirement for all clinicians involved in specimen packaging to adhere to the International Air Transportation Association (IATA) Dangerous Goods Regulations and undertake training in IATA Handling and Shipping of Biological Substances (Cat B) and/or Dangerous Goods.[21] Although provided by Queensland Health, this course is not free of charge to Hospital and Health Services, and in my position as Nursing Director of the Torres and Cape TB Control Unit, I approved immediate access to the course for my team and contacted PHC Health Centre Managers to notify them of the mandatory requirement and to identify other clinicians that would benefit from the training. Many clinicians are now certified in the correct and safe packaging processes of specimens collected from isolated areas.

The Torres and Cape TB Control Unit initiated further training based on findings from both Chapter 3 and 6 (paediatric TB). Once it was identified within this research that a small proportion of paediatric patients had been diagnosed as a result of using nasopharyngeal and nasogastric aspiration, training in both collection modalities commenced. While both collection modalities had been used in outpatient settings in the region, the Torres and Cape TB Control Unit aligned the training with evidence-based practice. It is now recommended that nasopharyngeal aspiration be implemented in outpatient settings and that nasogastric aspiration be implemented in hospital-based inpatient settings. An overnight stay in hospital allows patients to swallow sputum, which can be collected using early morning nasogastric aspiration prior to gastric emptying occurring. Further, after the Torres and Cape TB Control Unit provided hospital-based training, nursing 'champions' within Thursday Island Hospital ward that were confident and proficient in sputum induction and nasogastric aspiration were identified to assist others in both procedures.

Chapter 3 identified which Torres Strait PHCs were involved in the diagnosis of PTB case distribution and Chapter 4 (drug-resistant TB) assembled all DR-TB cases identified over time.

As a result of both studies, the Torres and Cape TB Control Unit implemented a two-yearly active case finding strategy for TCHHS employees stationed on Saibai Island as the location of highest risk of cross-border TB transmission.

Chapter 4 – Drug-resistant TB

In an effort to slow the risk of treatment delay described in Chapter 4.3, the PNG National Initial Visit form used to document TB risk, signs and symptoms, and other relevant medical history (Appendix J3)[8] was updated (Appendix J11)[11] to provide a space for clinicians to document if a PNG patient with presumptive TB had stayed with a resident of the Torres Strait Islands since becoming symptomatic. In the event that a PNG national is diagnosed with active TB disease, this additional information now allows the Torres and Cape TB Control Unit to immediately activate screening of close contacts. The same form also collects contact tracing information of PNG nationals and although this information is always shared with the TB Programme at Daru, contact screening at the time of writing is not available in the PNG villages adjacent to the Torres Strait. However, this may change now that a new level 3 health facility has been opened in Treaty village Mabadauan in PNG which can now provide a broad range of medical services.[58]

Chapter 4.4 identified a high proportion of patients with extrapulmonary involvement which prompted a revamp of the mode of delivery of TB education provided to clinicians working in PHCs in the TSPZ. Since 2019, TB education provided to clinicians working in the outer islands of the TSPZ has been based on the risk profile of each island. For example, if the Torres and Cape TB Control Unit identifies an increase in TB meningitis cases presenting to a particular island, then in-service training sessions on recognising and managing TB meningitis are now provided for staff in the relevant island cluster.

Chapter 4.4 demonstrated that a high proportion of patients diagnosed with TB/HIV coinfection experienced unfavourable TB outcomes. Just prior to the completion of this study, there was some discussion in the Torres and Cape TB Control Unit about the benefit of continuing to perform HIV tests in presumptive TB cases, particularly as HIV is unlikely to be a contributing factor in TB transmission in the region. As a result of this study, it was decided that HIV testing will remain part of the TB screening process in the Torres Strait for PNG nationals. Residents of the Torres Strait and Cape York communities will also continue to be tested for HIV, but only after confirmation of TB disease.

Chapter 5 – High Price

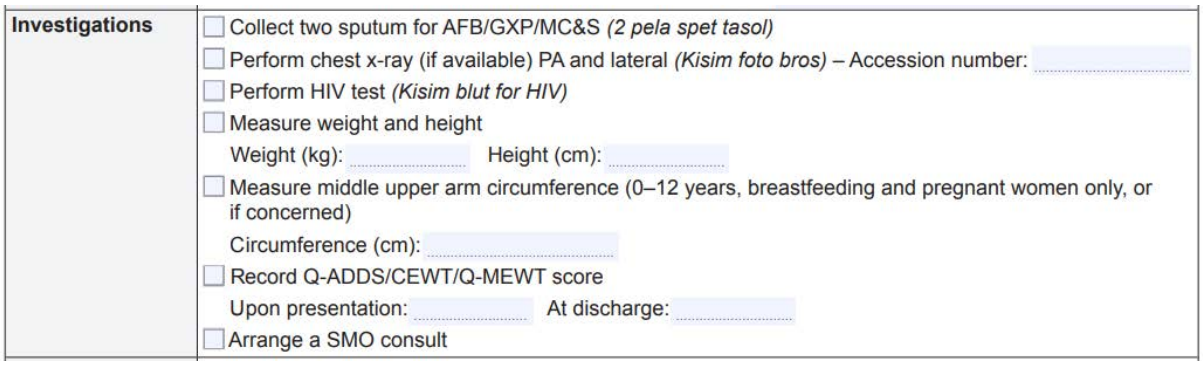
At the time the results from Chapter 5.1 were published, the estimates of the cost to manage PNG national patients accessing health services in the TSPZ and requiring aeromedical evacuation, were only partially accurate. As a result, I sent a copy of the pre-print of the relevant article (59) to the Strategic Policy Unit within the Queensland Department of Health who are responsible for submitting NPA funding requests to the Australian Commonwealth Department of Health. I also submitted the link to the pre-print to the Federal Member for Leichhardt and am hopeful that the evidence provided will lead to appropriate funding allocation which includes acknowledgment of costs borne by the Aeromedical Retrieval and Disaster Management Branch.

The gathering of evidence and the publication of real-time accurate data and details of the cost to provide aeromedical evacuation for PNG nationals shows the true distribution of funds spent by stakeholders. It also demonstrates the following:

1. TCHHS are not responsible for the majority of costs associated with providing care to PNG nationals.
2. Funds allocated by the Commonwealth Department of Health are not wholly being used for the purpose for which they were intended within the NPA. The NPA stipulates that funding is to be allocated to TB control but the Torres and Cape TB Control Unit who are responsible for TB control in the region have no access to or visibility of any of these funds.
3. Hospital and Health Services which provide care to PNG nationals that do not enter Queensland Health facilities via the TSPZ are not eligible to receive funding associated with this NPA.

Chapter 5.2 identified an absence of some discharge scores being recorded in patient information systems and the ethical implications of this. The Torres and Cape TB Control Unit has amended the local TB screening procedure for the management of presumptive TB cases to include a Q-ADDS/CEWT/Q-MEWT score at both presentation and at discharge. Although a discharge score is a requirement within existing policies and procedures, it was not previously embedded in the PNG National Initial Visit form (Appendix J3)[8] which clinicians complete during patient assessment. Although this edit may not immediately result in the discharge score being provided on the TB screening form, any absence in this data collection point will prompt

a nurse from the Torres and Cape TB Control Unit to follow up. This will enable real-time oversight of adherence to aeromedical retrieval policy and assist with future audits. The new Initial Visit form (Appendix J11)[11] now also includes a prompt and space to record middle upper arm circumference and height for paediatric patients.



Investigations	☐ Collect two sputum for AFB/GXP/MC&S *(2 pela spet tasol)* ☐ Perform chest x-ray (if available) PA and lateral *(Kisim foto bros)* – Accession number: ..... ☐ Perform HIV test *(Kisim blut for HIV)* ☐ Measure weight and height Weight (kg): ..... Height (cm): ..... ☐ Measure middle upper arm circumference (0–12 years, breastfeeding and pregnant women only, or if concerned) Circumference (cm): ..... ☐ Record Q-ADDS/CEWT/Q-MEWT score Upon presentation: ..... At discharge: ..... ☐ Arrange a SMO consult

Figure 7.1.5 Translational research – excerpt from the new (2021) Initial Visit form used at the Torres Strait / PNG border for PNG national patients presenting with presumptive TB (Appendix J11).[11]

Given the patient safety implications identified in the findings of Chapter 5.2, a copy of the audit was provided to various Executives and Directors in TCHHS in real-time. It is expected that the findings and research output from Chapter 5.2 will lead to the most significant changes in the way presumptive TB is managed at the border.[60]

As a result of being both an employee and researcher within the TCHHS, the Health Service Chief Executive received a copy of all manuscripts within this thesis prior to submission to journals.

Chapter 6 – Paediatric TB

A high proportion of paediatric patients that fell beneath the third percentile for age and weight was identified in Chapter 5.2 and further investigated in Chapter 6. As a result of these findings, the Torres and Cape TB Control Unit, consulted with expert TB paediatricians in Queensland and added middle upper arm circumference measurement to the PNG National Initial Visit form.[11] Per expert advice, this measurement is now required for patients aged 0-12 years, or patients that are breastfeeding or pregnant, or in circumstances where clinicians are concerned. The Torres and Cape were further supported in implementing these policy changes through the Australian Respiratory Council who provided measuring tapes for distribution to the outer islands. Height in centimetres was also added to the TB screening tool to enable calculation of

body mass index, which is a measurement index used for at-risk presumptive TB patients in other settings.[61,62]

7.6 Recommendations and Further Research

7.6.1 Initiatives that could be implemented in the future to improve tuberculosis management in the Torres Strait/Papua New Guinea region, and recommendations for future research

> The arc of the moral universe bends towards justice. Together, we bend it faster.
>
> - Theodore Parker, 1871; Partners in Health – in Documentary: "Bending the Arc"[43]

Chapter 2

This research has significantly contributed to future research opportunities with the creation of four distinct and deidentified databases pertaining to TB case notifications in the Torres Strait / PNG region over two decades. These databases are a product of the amalgamation of multiple data sources and provide the most up to date and accurate subset of TB data available in Queensland. With appropriate permissions, future researchers will be able to access these datasets.

Chapter 3

Recommended initiative:

1. Implementation of a decentralised Xpert Ultra® on Saibai and / or Thursday Island.
2. Incorporation of Xpert extensively drug-resistance (XDR) cartridge would offer added understanding to DR-TB resistant patterns and identify the region's first cases.
3. Training modules on clinical recognition of TB as well as fine needle aspiration, induced sputum, nasopharyngeal aspiration and nasogastric aspiration should be incorporated into mandatory training programs for nurses working in the Torres Strait Islands.
4. Consideration of alternative specimen collection methods that do not require sputum such as oral tongue swabs.

Future research:

1. Cost and feasibility study of a decentralised Xpert Ultra® as the frontline diagnostic test in the Torres Strait Islands with high rates of drug-resistant TB.

2. Further research to understanding why young children were so proficient at voluntary expectoration in this study to improve future efforts in quality sputum collection.

Chapter 4

Chapter 4.1

Recommended initiative:

1. TB training in the Torres Strait Islands to include evidence of heightened MDRTB risk for females, and for residents of Mabadauan, Ture Ture and Daru to promote an increased index of suspicion in these high-risk groups.

Future research:

1. Qualitative research exploring the role of women in caring for MDR-TB patients in PNG villages adjacent to the Torres Strait Islands to ascertain possible reasons for association between females and MDR-TB.
2. Qualitative ethnographic research exploring the effects of movement, social and cultural constructs to help explain the presence of DR-TB 'hot-spots' next to neighbouring non hot-spots and the social-cultural drivers of TB transmission.
3. Qualitative research exploring barriers to treatment adherence in PNG villages.

Chapter 4.2

Recommended initiative:

1. TB Unit to continue to work with the Cross Border Communication Officer to ensure the rapid transfer of patients to Daru and work with the TB Programme at Daru to promote transparency of patient outcomes.

Chapter 4.3

Future research:

1. Prospective study into why new cases were more likely to be treated sooner than previously treated cases.
2. Retrospective study of factors that contribute to specific variables reflecting the time to commencement of effective treatment delay (patient delay, health system delay;

treatment delay) to provide evidence that supports refined and focused initiatives on areas of high-need.
3. Prospective study of factors that contribute to treatment delay in patients with both DR-TB and DS-TB.

Chapter 4.4

Recommended initiatives:

1. Collect baseline bloods from patients with presumptive TB to assist with determining casual pathways. Baseline laboratory testing to detect diabetes mellitus, cytopenia, HIV, and liver disease are likely to assist clinicians in effectively managing TB treatment and foreseeing complications.
2. TB Unit to establish collegial relationships with diabetes, renal and sexual health teams to enhance screening opportunities and help reduce unfavourable outcomes in coinfected patients.
3. TB Unit to continue to maintain collegial relationships with Daru and enhance cross-border collaboration to protect patients from unfavourable outcomes.

Future research:

1. Qualitative research exploring why close contacts of known TB cases were protected from unfavourable outcomes, and if they are accessing health services earlier than patients who are not close contacts.

Chapter 5

Chapter 5.1

Recommended initiatives:

1. To achieve optimal transparency for taxpayers, Australian Government Department of Health funds designated for aid in the management of cross-border patients should be held separately in HHS funding portfolios.
2. As the service provider for TB control, the Torres and Cape TB Unit should be involved in providing milestone reporting on NPA funding.

3. Australian Government Department of Health should consider funding allocation appropriate to funds spent, with consideration for contributing stakeholders that are not currently funded via the NPA.
4. The Queensland Government Department of Health should use and expand on the baseline provided in this study to develop health economic models that lead to sufficient attainment and distribution of funds for the safe and ethical management of PNG nationals that present to PHCs in the TSPZ.

Future research:

1. Cost analysis and review of milestone reports to determine how the 2012-2016 and 2016-2020 NPA funds were spent.

Chapter 5.2

Recommended initiatives:

1. Required orientation and training of all staff to adequately address complex operational challenges associated with remote health care delivery, including ethical and medico-legal issues associated with time-critical health emergencies.[63]
2. In addition to identification of patient deterioration using current early warning tool scores, implementation of clinical algorithms that are appropriate for TB patients and malnourished children.[64]
3. Ongoing monitoring and evaluation to ensure transparency and justice.[65] Outcomes shared with local stakeholders will promote greater transparency of decision-making, with rapid identification of skills shortages, deviations from policy or policy limitations with continuous service improvements led by frontline nurses and clinicians.[65]
4. Care pathways that include documenting a set of vital signs just prior to discharge and with medical review for CEWT / Q-ADDS / QMEWT scores ≥5, may improve patient outcomes and visibility of deviating vital signs.[66] An automated notification within existing health system software may be beneficial to a) prompt clinicians to collect and record vital signs at discharge and b) reduce deviations from policy and procedures.[67]
5. Greater transparency into how ‘ceiling of care’ decisions are made for cross-border PNG patients seeking healthcare via the TSPZ.
6. Consideration of points allocated within existing CEWT / Q-ADDS / QMEWT for critical pathology.

7. Sufficient knowledge, training, and experience in the management of malnutrition is required for nutritionists working in the Torres Strait region.
8. In the Torres Strait, medical assessments frequently involve a discussion between a doctor at Thursday Island Hospital and the island nurse on duty and decisions are hence based on information shared during these exchanges (which may incorporate clinical assessment, vital signs or point of care test results). Decisions being made by medical officers under these circumstances include whether to order medical interventions, approve aeromedical evacuation or commence treatment. In traditional hospital-based and general practitioner settings, medical officers use all their senses to assess and evaluate the condition of a patient. In remote settings, in-person consultations are substituted by telehealth, and remote patient assessment, monitoring and point of care testing is provided by nurses and Indigenous Health Workers employed in the PHCs. [68] In the Torres Strait, videoconferencing capability is available in all PHCs. The Royal Australian College of General Practitioners recommends video consultations over telephone consultations for complex patients.[69] Hence, consideration of a change to local policy is indicated whereby video consultation with a medical officer should be available for patients that meet aeromedical evacuation criteria.

Future research:

1. Exploring factors that influence both nurse's and physician's responses to patient deterioration and how peer-modelling may improve health care delivery and adherence to policy.[52,70]
2. Qualitative research on patient experiences when presenting to PHCs in the Torres Strait and whether informed consent was obtained.
3. Quality of communication between clinicians was not evaluated in this study but given its potential impact on patient outcomes, further research on this issue is warranted.[50,53]

Chapter 6

Recommended initiatives:

1. Obtain approval to train clinicians in fine needle aspiration in remote settings to improve diagnostic yield in paediatric patients with lymph TB.
2. By expanding current TB screening tools to include middle upper arm circumference and height for BMI calculations, clinical algorithms that are appropriate for malnourished

children with TB can be developed. Given the high costs of aeromedical retrievals, tools that are suitably sensitive with reasonable specificity for patients at risk of death and used by decision makers, may lead to a higher proportion of patients that are medically evacuated but may ultimately improve mortality rates.

Future research:

1. Development, piloting, and validation of a paediatric TB diagnostic scoring tool specific to this population is required.
2. To provide a baseline for age/weight of PNG nationals presenting to health facilities in the TSPZ, and validate paediatric malnutrition, a large population survey in both malnourished and non-malnourished children is required. As age/weight percentiles in children of industrialised countries may not detect ecological and genetic differences that may be relevant to the coastal children of PNG,[71] a joint collaboration between the TCHHS and Daru General Hospital will allow for greater numbers of participants.
3. An early warning scoring tool that is specific to paediatric TB patients in the region is required. To assess utility of such a tool, a formal prospective study that incorporates critical triage points is required.
4. Research into why the median length of stay for PNG nationals attending Cairns Hospital is significantly greater than Townsville and Thursday Island Hospitals.

7.6.2 Reflection

Health policy formulation and implementation in the Torres Strait / PNG border region requires locally-based evidence and an understanding of local policy constraints. Although there are regulatory frameworks within Queensland Health which reflect the WHO End TB Strategy,[1] this thesis has provided scientific evidence that challenges local policy formation and implementation, and illustrates examples of policy governance and adherence failures. At the top of the hierarchy are many domestic and international stakeholders that may engage in and help determine local policy decision frameworks.[72] At the other end of the hierarchy are the clinicians on the ground who must find a balance between the likelihood of patient deterioration, hierarchical pressure, and their moral obligations. The TCHHS should strive to formulate policy that protects lives and is sustainable and transparent, developing strong health systems to support this framework.[73] Threats to such a framework include the workplace culture of “collective truth” which undermines good policy and may develop over time. Such

"collective truths" may override clinicians' perceptions of their own autonomy in decision-making.[74]

The contents of the 'collective truth' may initially seem highly intuitive and reasonable,[75] until it is so ingrained as accepted practice that it goes unquestioned as it begins to violate human rights.[76] An example of this is "that PNG nationals should be treated by the PNG health system" – on the face of it is a perfectly reasonable "collective truth". Taken to an extreme conclusion, we have evidence of patients referred back to the PNG health system from Australia who die before reaching care in PNG. Some of these patients had clear warning signs while seeking care in the Australian health system.

This has led me to consider: At what point does the autonomy of medical practice stop and authority go unquestioned?[74] How is this ethical in a sub-set of society that may not have the means or the know-how to respond to inequities?

It might just be that philosophy -in particular the study of ethics- is the antidote to poor patient outcomes at the Australia / PNG international border.[74] There is room for a philosophical approach which can both illustrate the implications of 'collective truth' and confused thinking, and lead to coherent practice and clear practical thinking.[74] Philosophy forces clarity and honesty, and exposes assertions deeply embedded in the day to day of clinical practice.[77] Questioning one's own moral character is generally not given too much thought because people generally understand their own fundamental values and assumptions.[78] Philosophy breaks open those fundamental values by forcing individuals to question their own assumptions, particularly in a clinical situation where thinking for oneself is no longer an option and where the 'collective truth' is governed by clinical direction that may derail critical thinking.[74,77] In examining structural inequities, where the workforce must contend with the burden of moral problems, it is possible that no one is thinking about the implications of the 'collective truth'.[74]

While I am incredibly proud of what I have managed to achieve in the Torres Strait as a result of the findings in this thesis, one question always remains. Is it ethical for us to provide this care? With very little governance and no consistent approach to cross-border healthcare, the situation is complex and fragile. As a clinician working in the Torres Strait for eight years, I understand the importance of multidisciplinary and cross-border collaboration. However, if just one person in the clinical team believes that Australia should not be funding healthcare for PNG nationals, or that PHCs in the Torres Strait should be reserved only for residents of Australia,

we run the risk of collectively violating human rights. It is my sincere hope for the future, that the evidence derived from within this thesis paves a path for improved healthcare, governance, beneficence, and research.

> Our prime purpose in this life is to help others, and if you can't help them, at least don't hurt them.
>
> - 14th Dalai Lama, Spiritual Leader of Tibet

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Appendices

Appendix A: Approvals

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Appendix B: Copyright Permissions

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Appendix C: Clinical Excellence Showcase 2021 Abstract

CLINICAL EXCELLENCE SHOWCASE

HOME ABOUT DOCUMENTARIES EVENTS IMPROVEMENT EXCHANGE PODCASTS WORKFORCE

Project Name	Improving outcomes for tuberculosis patients in the Torres Strait / Papua New Guinea border region
HHS:	Torres and Cape HHS
Initiative:	Service improvement
Presented by:	Ms J'Belle Foster

COVID-19 brought the closure of the international border between Australia and Papua New Guinea (PNG). Fearful of the foothold that TB may take in PNG villages during this time, and the TB transmission risk this poses to residents of the Torres Strait, the Torres and Cape TB Control Unit have undertaken extraordinary measures to use locally-derived data to improve TB service delivery in our region.

Appendix D: Funding

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Appendix E: Chief Executive Signed – Support for article publication

Appendix F: Continuous Quality Improvement Award

Appendix G: Professional Development

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JAMES COOK UNIVERSITY AUSTRALIA

Assoc Prof Melissa Crowe
BSc(Hons), PhD
Head, Cohort Doctoral Studies Program

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8 April 2022

Dear Liz,

This is to verify that J'Belle Foster of Cohort 10 has attended eight Cohort Block weeks since she commenced with the Cohort Doctoral Studies Program in February 2016. She has therefore completed 158 hours of professional development with the Cohort Doctoral Studies Program.

Kind Regards

Melissa Crowe, PhD
Head, Cohort Doctoral Studies Program
Division of Tropical Health and Medicine

RM

Redman-MacLaren, Michelle <michelle.maclaren@jcu.edu.au>

To: J'Belle Foster

Tue 15/03/2022 3:11 PM

Cc: CMD Research <cmd.research@jcu.edu.au>; Moxon, Joseph; Dean CMD <deancmd@jcu.edu.au>

Dear J'Belle,

I write to congratulate you on being the successful applicant to represent the CMD HDR community! You wrote a convincing application and we in the CMD Research team felt that the HDR rep role would further extend your already impressive skills set in leadership and advocacy.

J'Belle, we look forward to your input at the bi-monthly Research and Research Education Committee (RREC) meetings, you connecting with HDR colleagues at the monthly CMD HDR Catch-up Up Zoom meetings, and you working with the ADRE and CMD Research team more broadly to provide advice from a HDR perspective.

Helen will send you the meeting invites for your calendar, and the terms of reference for the RREC. The HDR rep appointment is not time bound - we can review after a year of 'repping' service and see how it has gone for you. If would like to step down at the end of a year you can, or if you prefer to stay on, that is fine too.

Again, congratulations J'Belle, and thank you again for your offer to serve the HDR community in our College.

Kind regards,
Michelle

Michelle Redman-MacLaren BSW, MSW, PhD
Associate Dean, Research Education
Senior Research Fellow

College of Medicine and Dentistry
Division of Tropical Health and Medicine
James Cook University, Australia

Appendix H: Data Charts

Appendix H1: Scoping Review – What are the common themes when managing TB under challenging circumstances?

Author / Year	Country	Type of Article	Over-crowding (Risk-based) (RB1)	Poor Nutrition (RB2)	Financial constraints (RB3)	Health Illiteracy (RB4)	Treatment Delay (RB5)	Comorbidities (RB6)	Climatic Difficulties (Programmatic Challenges) (PC1)	Geographical Difficulties (PC2)	Damaged Health Infrastructure (PC3)	Limited Human Resources for Health (PC4)	Insecurity (PC5)	Treatment Interruptions (PC6)	Disrupted Health Services (PC7)	Access (PC8)	Allocation of Financial Resources (PC9)	Cross Border (PC10)	Setting
(Aberle et al., 2007)	Croatia	Original research	1	0	1	0	1	0	0	0	1	1	1	1	1	0	0	0	Post-conflict
(Accorsi et al., 2001)	Northern Uganda	Original research	0	1	1	0	0	1	0	0	0	0	1	0	0	1	0	0	Conflict
(Acosta, Kaluski, & Dara, 2014)	Ukraine	Commentary	1	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1	Conflict
(Agutu, 1997)	Somalia	Original research	0	0	1	0	0	1	0	0	0	0	1	0	0	1	0	1	Remote, Conflict
(Ahmad, 2001)	Afghanistan	Editorial	0	1	1	1	0	0	0	0	0	1	1	1	1	0	1	1	Conflict
(Ahmadzai et al., 2008)	Afghanistan	Original research	0	0	0	0	1	0	1	1	1	1	1	0	1	1	0	0	Post-conflict
(Ai et al., 2010)	China	Original research	0	0	1	0	0	1	0	0	0	0	0	1	0	1	0	0	Remote
(Alene, Viney, McBryde, & Clements, 2017)	Ethopia	Original research	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	1	Cross border
(Ali-Gombe & Onadeko, 1997)	Africa	Original research	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	High burden countries
(Alvarez et al.,	Canada	Original research	0	0	0	1	0	0	0	1	0	0	0	0	0	0	1	0	Remote /

2016)																		Indigenous health
(Alvarez et al., 2015)	Canada	Original research	0	0	0	0	1	0	1	1	0	0	0	0	0	0	0	Remote / Indigenous health
(Alvi, Hussain, Shah, Khalida, & Shamsudin, 1998)	Pakistan	Original research	1	0	0	1	0	0	0	1	0	0	0	0	1	1	1	0	Remote
(Ansumana et al., 2017)	West Africa	Literature review	0	0	0	0	0	1	0	0	0	1	0	1	1	0	1	0	Ebola epidemic
(Armstrong, Das, Mansoor, Babu, & Isaakidis, 2014)	India	Original research	0	0	0	0	0	0	1	0	0	0	1	1	1	1	0	1	Conflict
(Awotula & Pelat, 2012)	West Africa	Literature review	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	Remote
(Baghaei, Marjani, Javanmard, Tabarsi, & Masjedi, 2013)	Global	Literature review	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	Global (general)
(Balbay, Balbay, Arbak, Annakkaya, & Bilgin, 2011)	Turkey	Original research	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	Natural disaster
(Bam, Enarson, Hinderaker, & Chapman, 2007)	Nepal	Original research	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	1	Post-conflict
(Barennes, Keophithoun, Nguyen, Strobel, &	Lao PDR	Original research	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	Remote

Odermatt, 2010)																		
(Bariety & Boulenger, 1943)	France	Original research	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	Conflict
(Barr & Menzies, 1994)	El Salvador	Original research	0	1	0	0	0	0	0	0	0	0	1	0	1	0	0	0	Conflict
(Barwise, Lind, Bennett, & Martins, 2013)	Mozambique	Original research	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	1	Cross border
(Bastian, 2005)	Indian Ocean region (Australia / Pacific)	Commentary	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	Global (general)
(Batungwanayo et al., 1992)	Rwanda	Original research	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	High burden country
(Benca et al., 2007)	Global	Literature review	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	Natural disaster / Conflict
(Bernitz, 2008)	Scandinavia	Original research	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	Cross border
(Bhatia, Dranyi, & Rowley, 2002)	India	Original research	1	1	0	1	1	0	0	0	0	0	0	1	0	0	0	0	Post-conflict
(Bieberly & Ali, 2008)	New Orleans	Original research	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	Natural disaster
(Bizuneh, 1980)	Ethiopia	Programme evaluation	1	1	1	0	0	0	0	0	0	1	1	1	0	0	0	1	Post-conflict
(Bloom, Hoxha, Sambunjak, & Sondorp, 2007)	Kosovo	Original research	0	0	1	0	1	0	0	0	0	1	1	0	0	1	1	0	Conflict

(Bodiang, 2000)	Global	Commentary	0	0	0	0	0	0	0	1	0	1	1	0	1	1	1	0	Post-conflict
(Bøhler, Mustafaa, & Mørkve, 2005)	Sudan	Original research	1	1	1	1	1	0	0	0	0	1	1	1	0	0	1	0	Post-conflict
(Bor & Epstein, 1991)	Global	Literature review	0	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	Global (general)
(Bourgeois, Fourestier, & Torre, 1944)	France	Original research	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Conflict
(Bowerman, 2015)	Alaska	Commentary	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	Remote
(Bowerman, Lin, & Huang, 2015)	Taiwan	Original research	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Remote
(Brooke, 1946)	Japan	Original research	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Post-conflict
(Burzynski et al., 2013)	USA	Programme evaluation	0	0	0	0	0	0	1	0	0	0	0	1	1	0	0	0	Natural disaster
(Cain et al., 2015)	East Africa	Literature review	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	1	Cross border
(Carniel et al., 2014)	Brazil	Original research	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	Remote
(Carpenter, 1950)	Germany post WW2	Commentary	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	Post-conflict
(Caselle & Galvagno, 1992)	Kenya	Original research	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	Remote
(Cegielski & McMurray, 2004)	Europe (wartime)	Literature review	1	1	0	0	0	1	0	0	0	0	0	0	1	0	0	0	Conflict

(Chaiyachati et al., 2013)	South Africa	Original research	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	0	Remote
(Chang, Simkin, De Lara, & Kirsch, 2016)	Philippines	Original research	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	Natural disaster
(Chapin, Daniels, Elias, Aspilcueta, & Doocy, 2009)	Southern Peru	Original research	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	Natural disaster
(Charles et al., 2017)	Haiti	Original research	1	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	Natural disaster
(Charles et al., 2014)	Haiti	Original research	0	1	1	0	0	1	0	0	1	0	0	0	0	0	1	0	Natural disaster
(Choi et al., 2007)	South Korea	Original research	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	Cross border
(Clark, Riben, & Nowgesic, 2002)	Canadian Indigenous	Original research	1	1	1	0	1	0	0	1	0	0	0	0	0	1	0	0	Remote
(Coninx, 2007)	Global	Literature review	0	1	0	0	0	1	0	0	1	0	1	1	1	0	1	0	Conflict / post-conflict
(Cookson et al., 2015)	Jordan	Original research	1	0	0	1	0	1	0	0	1	1	1	1	1	1	1	1	Post-conflict
(Cousins, 2014)	Syria	Editorial	1	0	0	0	0	0	0	0	1	1	0	1	1	0	0	1	Post-conflict
(Cowan et al., 2016)	Mozambique	Programme evaluation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	High-burden country
(Cross et al., 2014)	Papua New Guinea	Original research	1	1	0	1	1	0	0	0	0	1	0	1	1	1	1	0	High-burden

																		country / Remote
(Crowle & Ross, 1989)	Global	Original research	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	Global (general)
(Cunha et al., 2014)	Brazil	Original research	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	Remote / Indigenous health
(Daniels, 1947)	Europe	Original research	1	1	0	0	0	0	0	0	1	1	0	0	1	0	0	0	Post-conflict
(Dara et al., 2012)	Europe	Literature review	0	0	1	0	0	0	0	0	0	0	0	1	0	1	0	1	Cross border
(Dara et al., 2016)	Europe	Commentary	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	1	Cross border
(Dara et al., 2017)	Global	Literature review	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	1	Cross border
(Das et al., 2014)	India	Original research	0	0	0	0	0	0	0	1	0	0	1	1	0	1	0	0	Conflict
(Datta et al., 2001)	India	Original research	1	0	1	0	0	0	1	1	0	0	0	0	0	1	0	0	Remote
(Davies, 1985)	Indian Sub-continent	Literature review	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	High burden country
(DeGraw et al., 2006)	New Orleans	Original research	0	0	0	0	0	0	1	0	1	0	0	1	1	0	0	0	Natural disaster
(Deiss et al., 2009)	Mexico	Original research	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	Cross border
(DeSisto et al., 2015)	USA-Mexico border	Original research	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	Cross border
(Devi et al., 2013)	India	Original research	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	Remote

(Di Perri et al., 1998)	Burundi-Rwanda border	Original research	0	1	1	0	0	0	1	0	0	0	1	0	0	0	0	1	Cross border
(Diefenbach-Elstob et al., 2017)	Papua New Guinea	Original research	0	1	1	0	1	0	0	1	0	1	0	0	0	1	0	0	Remote
(Dierberg et al., 2016)	India	Original research	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Remote
(Dobler, Flack, & Marks, 2012)	Australia	Original research	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	TB/DM
(Doganay & Demiraslan, 2016)	Turkey	Literature review	1	1	0	0	0	0	0	0	1	0	1	0	1	0	1	1	Conflict
(Dogba, Cadmus, & Olugasa, 2014)	Liberia	Original research	1	0	0	0	0	0	1	0	0	0	1	0	0	0	1	1	Post-conflict
(Doğru & Döner, 2017)	Syria	Original research	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	1	Post-conflict
(Domercant, Guillaume, Marston, & Lowrance, 2015)	Haiti	Editorial	0	0	0	0	0	0	1	0	0	1	0	0	0	0	1	0	Natural disaster
(Donnan, Coulter, Simpson, Clark, & Nourse, 2017)	Australia	Original research	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	Cross border
(Dowell, Tappero, & Frieden, 2011)	Haiti	Editorial	0	0	0	0	0	0	1	0	1	1	0	1	1	0	0	0	Natural disaster
(Drobniewski &	Global	Literature review	1	1	0	0	0	0	0	0	0	0	1	0	1	0	0	0	Post-

Verlander, 2000)																		conflict
(Dudnyk, Rzhepishevska, Rogach, Kutsyna, & Lange, 2015)	Ukraine	Editorial	1	0	0	0	0	0	0	0	1	1	1	0	1	1	1	0	Conflict
(Dummer & Cook, 2007)	China	Literature review	0	0	1	0	0	0	0	0	0	1	0	0	0	1	1	0	Remote
(Dyck et al., 2007)	Canadian Indigenous	Original research	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	TB/DM
(Ekaza et al., 2013)	Cote D'Ivoire	Literature review	0	0	1	0	1	1	0	0	1	0	1	0	1	1	1	0	Conflict
(Elden et al., 2011)	Swaziland	Original research	0	0	1	0	0	1	0	1	0	1	0	0	0	0	0	0	Remote
(Eriki, 1988)	Uganda	Original research	1	1	0	0	0	1	0	0	0	0	1	0	0	0	0	0	Conflict
(Ewart, 1882)	India	Editorial	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	Remote
(Fares, 2011)	Global	Literature review	0	1	0	0	1	0	1	0	0	0	0	0	0	0	0	0	Global (general)
(Faurholt-Jepsen et al., 2011)	Tanzania	Original research	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	High burden country
(Felten & Forte, 1995)	former Yugoslavia	Programme report	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	Conflict
(Fiebig et al., 2017)	Austria/Romania/Germany	Original research	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	Cross border
(Figueroa-Munoz & Ramon-Pardo, 2008)	Global	Editorial	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	Cross border

(Finnie et al., 2010)	South Africa	Original research	0	0	1	1	1	1	0	0	0	0	0	1	0	1	1	0	Remote
(Fochsen, Deshpande, Ringsberg, & Thorson, 2009)	India	Original research	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	Remote
(H. Ford & Wright, 1994)	Swaziland	Original research	1	1	1	1	1	1	1	0	0	0	0	0	0	1	0	0	Remote
(N. Ford, Sizaire, & Mills, 2008)	Global	Editorial	1	1	0	0	0	1	0	0	0	0	1	1	0	1	0	0	Natural disaster / Conflict
(Furin & Mathew, 2013)	Haiti	Editorial	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	Natural disaster
(Galvin, 2000)	East Timor	Editorial	1	1	0	0	0	0	0	0	1	1	0	0	1	1	1	1	Post-conflict
(Gardner, Rohde, & Majumdar, 1972)	Bangladesh	Original research	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	Post-conflict
(Gele, Bjune, & Abebe, 2009)	Ethiopia	Original research	0	0	1	1	1	0	0	0	0	0	1	0	1	1	1	0	Conflict
(Gele & Bjune, 2010)	Ethiopia	Original research	0	0	1	1	1	0	0	0	0	0	0	0	0	1	1	0	Remote
(Gele, Sagbakken, Abebe, & Bjune, 2010)	Ethiopia	Original research	0	0	1	1	1	0	1	1	0	1	1	0	1	1	0	0	Remote
(Getahun, Harrington, O'Brien, & Nunn, 2007)	Global	Literature Review	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0	0	High burden countries

(Gibson, Boillot, & Jalloh, 1998)	Sierra Leone	Original research	1	1	1	1	1	0	0	0	1	0	1	1	0	1	1	0	Conflict
(Githui et al., 2000)	Kenya	Original research	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	Conflict
(Glass et al., 1980)	Cambodia refugees in Thailand	Original research	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	Cross border
(Goe & Linton, 2005)	North Korea	Programme report	0	1	0	0	0	0	1	1	0	0	0	1	0	0	1	0	Remote
(Grace & Chenhall, 2006)	Australia	Original research	1	1	0	1	1	0	1	1	0	1	0	0	1	1	1	0	Remote
(Gupta, Gupta, Atreja, Verma, & Vishvkarma, 2009)	Global	Literature review	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	Global (general)
(Gurjav et al., 2015)	Trans-Siberian Railway	Original research	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	Cross border
(Gustafson et al., 2001)	Guinea-Bissau	Original research	0	0	0	0	1	1	0	0	1	0	1	1	0	1	0	0	Conflict
(Hale, 2002)	Zambia	Editorial	0	0	0	1	0	0	0	0	0	1	0	1	0	0	1	0	Post-conflict
(Hall et al., 2015)	Timor-Leste	Original research	0	0	1	0	0	0	1	1	0	0	0	0	0	1	0	0	High burden country
(Harper, Fryatt, & White, 1996)	Nepal	Original research	1	0	0	0	0	0	0	1	0	1	0	0	0	1	1	0	Remote
(Harris, Eyles, Penn-Kekana, Thomas, & Goudge, 2014)	South Africa	Original research	0	1	1	0	0	1	0	0	0	1	0	1	0	1	1	0	Post-conflict

(Hehenkamp & Hargreaves, 2003)	South Sudan	Programme report	0	1	0	0	0	0	1	0	0	1	1	1	1	1	0	0	Conflict
(Hemhongsa et al., 2008)	Thailand-Myanmar border	Original research	0	0	0	0	0	1	0	0	0	0	1	0	0	1	1	1	Conflict
(Heng & Key, 1995) .	Cambodia	Editorial	0	1	1	0	0	0	0	0	1	1	1	1	0	0	1	1	Conflict
(Hernández Sarmiento et al., 2013)	Colombia	Original research	0	0	1	1	1	0	0	0	0	0	0	0	0	1	0	0	Remote / Indigenous health
(Heymann, Chen, Takemi, Fidler, & Tappero, 2015)	Global	Editorial	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	Ebola epidemic
(Hickson, Mercer, & Lokuge, 2012)	Australia/PNG	Original research	0	0	0	0	1	0	0	1	0	1	0	0	0	1	0	1	Cross border
(Hill & Eang, 2007)	Cambodia	Editorial	0	0	1	0	0	1	0	1	1	1	1	1	1	1	1	0	Post-conflict
(Hirota et al., 1977)	Nepal	Programme report	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	High burden country
(Hoffman et al., 2010)	Kenya	Original research	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	High burden country
(Honarvar et al., 2014)	Iran	Original research	1	0	1	0	1	0	1	0	0	0	0	1	0	1	0	0	Remote
(Houston, 1998)	Global	Editorial	1	1	1	0	0	1	0	0	0	1	1	0	0	1	1	0	Conflict
(Huong et al.,	Vietnam	Original research	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	High

2005)																		burden country
(Huong et al., 2007)	Vietnam	Original research	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	High burden country
(Ibrahim & Laaser, 2002)	Pakistan	Commentary	0	0	1	0	0	0	0	0	0	0	0	1	1	0	1	1	Conflict
(Ikram et al., 2014)	Afghanistan	Programme report	0	0	0	0	1	0	0	0	0	1	1	1	0	1	1	0	Post-conflict
(Ismail et al., 2016)	Syria	Literature review	1	1	0	0	0	0	0	0	1	1	1	1	1	1	0	1	Conflict
. (Ivers & Ryan, 2006)	Global	Literature review	1	0	0	0	0	0	1	0	1	0	0	1	1	0	0	0	Natural disaster
(Janssen, Grobusch, & Heller, 2013)	Gabonese Republic	Original research	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	Remote
(Jarallah, 1993)	Afghani refugees in Pakistan	Original research	0	0	1	1	0	0	0	0	0	0	1	1	0	1	0	0	Conflict
(Jean & Weise, 1974)	Haiti	Programme evaluation	0	0	0	0	0	1	1	0	1	0	0	0	1	0	0	0	Natural disaster
(Jean-Louis et al., 2017)	Haiti	Original research	0	0	1	1	1	0	1	1	0	1	0	1	0	1	0	0	Rural
(Jeon & Murray, 2008)	Global	Literature review	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	Global (general)
(Jochem et al., 1997)	Nepal	Original research	0	0	0	0	0	0	0	1	0	1	0	1	0	1	0	0	Remote
(Johnson & Ellner, 2000)	Global	Literature review	1	1	1	0	0	1	0	0	0	0	1	1	0	0	1	1	High burden countries

(Jonaidi Jafari, Radfar, & Ghofrani, 2007)	Iran	Original research	1	1	0	0	0	0	1	0	1	0	0	1	1	1	0	0	Natural disaster
(Jurčev-Savičević et al., 2011)	Croatia	Original research	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	1	Post-war
(Kaboru et al., 2013)	Democratic Republic of the Congo	Original research	0	0	0	0	0	1	0	0	1	0	1	1	0	0	1	1	Conflict
(Kanamori, Aso, et al., 2013)	Japan	Original research	1	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	Natural disaster
(Kanamori et al., 2012)	Japan	Original research	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	Natural disaster
(Kanamori et al., 2016)	Japan	Original research	1	1	0	0	1	1	0	0	1	0	0	1	0	1	0	0	Natural disaster
(Kanamori et al., 2014)	Japan	Original research	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	Natural disaster
(Kanamori, Uchiyama, et al., 2013)	Japan	Commentary	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	Natural disaster
(Karki, Kittel, Bolokon, & Duke, 2017)	PNG	Original research	1	1	1	0	1	0	1	1	0	0	0	1	0	1	0	0	Remote
(Karyadi et al., 2000)	Indonesia	Original research	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	High burden country
(Kasis et al., 2001)	Ethiopia	Programme evaluation	1	1	1	0	1	1	0	0	0	1	0	0	0	1	0	0	Natural disaster / Remote
(Keehn, 1980)	US veterans from Korean	Original research	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	Post-conflict

	and WW2																	
(Kessler, Connolly, Levy, Porter, & Rieder, 1998)	Global	Literature review	1	1	0	0	0	1	0	0	0	1	0	1	0	0	1	0	Conflict
(Keus, Houston, Melaku, & Burling, 2003)	South Sudan	Original research	0	0	0	0	1	1	1	0	0	0	1	1	1	1	0	0	Conflict
(Kevany et al., 2012)	South Sudan	Literature review	0	0	0	0	0	0	0	0	0	1	1	0	1	0	1	0	Post-conflict
.																			
(Kevany et al., 2014)	Iraq	Original research	0	0	0	0	0	0	0	1	0	0	1	0	0	1	0	1	Post-conflict
(F. A. Khan, Smith, & Schwartzman, 2010)	Haiti	Editorial	1	1	0	0	0	1	1	0	1	0	1	0	1	1	1	0	Natural disaster
(I. M. Khan & Laaser, 2002)	Afghanistan	Programme evaluation	1	1	1	0	1	0	1	0	0	1	1	1	1	1	1	1	Conflict
(Khazei, Jarvis-Selinger, Ho, & Lee, 2005)	Tanna Island	Original research	0	0	0	0	0	0	0	1	0	1	0	0	0	1	1	0	Remote
(Kibuga, 2001)	Kenya	Programme evaluation	0	0	0	0	0	1	0	0	0	1	0	0	0	0	1	0	High burden country
(Kimbrough, Saliba, Dahab, Haskew, & Checchi, 2012)	Global	Literature review	1	1	1	0	1	1	0	0	1	0	1	1	1	1	0	0	Conflict / Natural disaster
(Koenig et al., 2015)	Haiti	Original research	1	1	1	0	0	1	0	0	1	0	0	1	1	0	0	0	Natural disaster
(Krieger & Moreau, 2002)	Global	Editorial	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	Remote

(Kuchuloria, Akhvlediani, & Akhvlediani, 2016)	Ukraine	Editorial	1	1	1	0	1	0	0	0	0	1	0	1	1	1	1	0	Post-conflict
(Kunimoto, Chedore, Allen, & Kasatiya, 2001)	Canada	Original research	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	Remote
(Kunst, 2017)	Europe	Editorial	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	Cross border
(Lainez, Todd, Ahmadzai, Doocy, & Burnham, 2009)	Afghanistan	Original research	1	0	1	1	1	0	0	0	0	0	0	0	0	1	0	0	Post-conflict
(Leblebicioglu & Ozaras, 2015)	Syrian refugees to Jordan, Turkey, Iraq and Lebanon	Editorial	1	0	0	0	0	0	0	0	1	0	1	0	0	0	0	1	Conflict
(Lee, Daya, Flickinger, & Jangchup, 2001)	India	Commentary	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	Remote
(Leeming-Latham, 2015)	Britain	Literature review	0	1	0	0	0	0	0	0	0	0	0	1	1	1	0	0	Post-conflict
(Lew, Vianzon, Garfin, & Hall, 2015)	Philippines	Programme evaluation	0	0	0	0	0	0	0	0	1	1	0	1	1	0	0	0	Natural disaster
(Li et al., 2013)	China	Original research	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	High burden country
(Li et al., 2014)	China	Original research	0	0	1	0	0	1	1	1	0	0	0	0	0	0	1	0	High burden

																		country
(Liddle, Elema, Thi, Greig, & Venis, 2013)	Somalia	Original research	0	1	0	0	1	0	0	0	1	1	1	1	1	1	1	0	Conflict
(Lin, Chongsuvivatwong, Geater, & Lijuan, 2008)	China	Original research	0	0	1	0	1	0	0	1	0	1	0	0	0	1	0	0	Remote
(Lô, Tall-Dia, Bonfoh, & Schelling, 2016)	Mauritania	Original research	0	0	1	1	0	1	0	0	0	0	1	0	0	1	1	0	Remote
(Ma et al., 2015)	Mongolia	Original research	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	High burden country
(Mackay, 1974)	Bangladesh	Original research	0	1	0	0	0	0	0	0	0	1	1	1	0	0	0	0	Conflict
(Mackey & Strathdee, 2015)	Ukraine	Commentary	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	Conflict
(Madebo, Lindtjørn, Aukrust, & Berge, 2003)	Ethiopia	Original research	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	High burden country
(Marais, 2016)	Global	Literature review	0	1	0	0	1	1	0	0	0	0	0	0	0	1	0	0	Global (general)
(Marais et al., 2013)	Global	Literature review	1	1	1	0	1	1	0	0	0	0	0	1	0	0	1	0	Global (general)
(Marche & Gounelle, 1950)	Europe Boer War, WW1 and WW2	Editorial	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Conflict
(Mariette, 1946)	USA	Editorial	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	Post-conflict

(Martin et al., 2005)	The Gambia	Original research	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	Remote
(Martins, Heldal, et al., 2006)	East Timor	Original research	0	0	0	0	1	0	0	0	1	1	1	1	1	0	0	0	Post-conflict
(Martins, Kelly, Grace, & Zwi, 2006)	East Timor	Original research	0	0	0	0	1	0	0	0	1	1	0	1	1	1	1	0	Post-conflict
(Masci & Bass, 2017)	West Africa	Book	0	0	0	0	1	1	0	0	0	1	0	1	1	1	1	0	Ebola epidemic
(Mashru, Kirlew, Saginur, & Schreiber, 2017)	USA	Original research	0	0	0	0	0	0	0	1	0	1	0	0	0	1	1	0	Remote
(Massey et al., 2012)	Solomon Islands	Original research	0	0	1	0	1	0	0	1	0	1	0	1	0	1	1	0	Remote
(Mastro & Coninx, 1988)	Thailand-Cambodian border	Programme evaluation	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	Conflict
(Masur et al., 2017)	Haiti	Original research	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	Natural disaster
(Matteelli, Centis, Sulis, & Tadolini, 2016)	Europe	Literature review	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	Cross border
(Mauch et al., 2010)	Global	Thesis	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	High burden countries
(M'Boussa, Yokolo, Pereira, & Ebata-Mongo, 2002)	Congo Brazzaville	Original research	1	1	0	0	0	1	0	0	0	1	1	1	1	1	1	0	Conflict

(McEwen, 2005)	USA-Mexico border	Original research	0	0	1	1	0	0	0	0	0	1	0	1	0	1	1	1	Cross border
(McGuire, 2017)	Kazakhstan	Literature review	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	Remote
(Mfinanga et al., 2005)	Tanzania	Original research	0	0	1	1	1	1	0	0	0	0	0	0	0	1	0	0	Remote
(Mikkelson, Snoke, Sharp, Westley, & Vall-Spinosa, 1973)	USA (Indigenous)	Original research	0	1	1	0	0	0	0	1	0	0	0	1	0	0	0	0	Remote / Indigenous health
(Miles, 1987)	Cambodia	Commentary	0	0	0	1	0	0	0	0	0	0	1	1	1	0	0	1	Conflict
(Miles & Maat, 1984)	Cambodia	Programme evaluation	1	0	1	1	0	1	0	0	0	0	0	1	0	0	1	1	Post-conflict
(Miner et al., 2010)	USA	Programme evaluation	0	0	0	0	0	0	1	0	1	0	0	1	1	0	0	0	Natural disaster
(Minetti et al., 2010)	Thailand-Myanmar border	Original research	0	1	1	0	1	1	0	0	0	0	0	1	0	0	0	1	Cross border
(Mitruka et al., 2014)	USA-Mexico border	Original research	0	0	0	0	1	1	0	0	0	0	0	1	0	1	0	1	Cross border
(Mochache & Nyamongo, 2009)	Kenya	Original research	0	0	0	1	1	1	0	0	0	0	0	1	0	1	0	0	Remote
(Mohamed, 1999)	Somaliland	Literature review	1	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	Post-conflict
(Moore, 1954)	Canada	Editorial	0	0	0	0	0	0	1	1	0	1	0	0	0	1	0	0	Remote / Indigenous health
(Moore-Gillon, 2000)	Global	Editorial	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	Post-conflict

(Moreno et al., 2017)	Not specified (modelling)	Original research	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	1	Cross border
(Moss et al., 2006)	Global	Literature review	1	1	0	0	0	0	0	0	0	1	0	1	1	1	1	0	Conflict / Natural disaster
(Mugerwa, 1998)	Africa	Editorial	1	1	0	0	0	1	0	0	1	0	1	0	0	0	0	0	High burden countries
(Myint et al., 2011)	Myanmar	Original research	1	1	0	0	1	0	1	0	1	0	0	0	1	1	0	0	Natural disaster
(Nakaji et al., 2004)	Japan	Original research	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	Seasonality
(Nelson, Naik, Tsering, & Cegielski, 2005)	India	Original research	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	Post-conflict
(Nevin, Silvestri, Hu, Tobler, & Trotta, 2008)	Afghanistan	Original research	1	0	0	1	0	0	0	0	0	0	0	0	1	1	0	1	Conflict
(Newitt, 1945)	USA	Editorial	1	1	1	0	1	0	0	0	0	1	0	0	0	0	1	0	Post-conflict
(H. T. M. Nguyen, Hickson, Kompas, Mercer, & Lokuge, 2015)	Australia/PNG	Original research	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	1	Cross border
(T. H. Nguyen, Odermatt, Slesak, & Barennes, 2009)	Lao PDR	Original research	0	1	1	1	0	0	0	0	0	0	0	0	0	1	0	0	Remote

(Nishimura, 2008)	Japan	Editorial	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	Post-conflict
(Noeske, Foe, & Kuaban, 2016)	Cameroon	Commentary	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	Cross border
(Odermatt et al., 2007)	Lao PDR	Original research	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	High burden country
(O'Keefe, 1983)	Zululand	Original research	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	Natural disaster
(O'Shea & Wilson, 2013)	Global	Literature review	1	1	0	0	0	1	0	0	0	0	0	0	1	1	0	0	Conflict
(Oxlade, Sugarman, Alvarez, Pai, & Schwartzman, 2016)	Canada	Original research	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	Remote
(Ozaras, Balkan, & Yemisen, 2016)	Syria	Commentary	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	Post-conflict
(Ozaras, Leblebicioglu, et al., 2016)	Syria	Literature review	1	1	1	0	0	0	1	0	1	1	1	1	1	1	1	1	Conflict
(Padmapriyadarsini, Narendran, & Swaminathan, 2011)	Global	Literature review	0	1	0	0	1	1	0	0	0	0	0	0	0	1	1	0	Global (general)
(Pan et al., 2015)	Global	Original research	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	High burden countries
(Panic & Panic, 2003)	Yugoslavia	Original research	0	0	1	1	1	1	0	0	0	0	0	1	0	0	1	0	Post-conflict
(Pape et al.,	Haiti	Literature review	0	1	0	0	0	1	0	0	1	1	0	0	0	0	0	0	Natural

2014)																		disaster
(Paquet & Hanquet, 1998)	Global	Literature review	0	1	0	0	1	0	0	0	0	1	0	0	1	0	1	0	Conflict
(Parpia, Ndeffo-Mbah, Wenzel, & Galvani, 2016)	West Africa	Original research	0	0	0	0	1	1	0	0	0	1	0	1	1	0	1	1	Ebola epidemic
(Pavlović et al., 1998)	Croatia	Original research	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Conflict
(Penaflor, 1954)	Philippines	Editorial	1	1	1	0	1	0	0	0	0	1	0	0	1	0	1	0	Post-conflict
(Plett, 2015)	Angola	Literature review	0	0	1	1	1	0	0	1	0	0	0	1	0	1	1	0	Post-conflict
(Ponthieu & Incerti, 2016)	Southern Africa	Literature review	1	0	1	0	0	1	0	0	0	1	1	1	1	1	0	1	Cross border
(Porter & Kessler, 1995)	Global	Literature review	1	1	0	0	0	1	0	0	0	0	0	1	0	0	0	0	Post-conflict
(Posner, 1951)	Polish and Latvian camp in UK post WW2	Original research	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Post-conflict
(Prost, 2008)	Tibetan diaspora in India	Original research	1	0	1	0	1	0	0	0	0	0	0	1	0	0	0	1	Post-conflict
(Prost, 2013)	Tibetan diaspora in India	Original research	1	1	1	1	1	0	0	0	0	0	0	1	0	1	1	0	Post-conflict
(Pushpalingam, 2001)	Ethiopia	Editorial	1	1	1	0	0	1	0	0	0	0	0	0	0	1	0	0	Post-conflict
(Qader et al., 2017)	Afghanistan	Original research	1	0	1	0	0	0	0	0	1	1	1	0	0	1	1	0	Post-conflict
(Qazizada & Safi, 1992)	Pakistan	Original research	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	Post-conflict
(Raviglione &	Global	Literature review	1	1	1	0	1	1	0	0	0	0	1	1	0	0	0	0	Global

Luelmo, 1996)																		(general)
(Ren, Sun, Wang, Ge, & Ye, 2015)	Philippines	Original research	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	Natural disaster
(Renzaho, 2007)	Mozambique	Original research	0	1	1	0	0	0	1	0	0	0	0	0	0	0	1	0	Post-conflict
(Reynolds, Turnidge, Gottlieb, & Moore, 2011)	Australia / PNG	Editorial	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	1	Cross border
(Rieder, 1985)	Cambodian refugees in Thailand	Original research	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	Post-conflict
(Rodger, Toole, Lalnuntluangi, Muana, & Deutschmann, 2002)	India	Original research	1	1	1	0	0	1	0	0	1	1	1	1	1	1	1	0	Conflict
(Rutta et al., 2001)	Tanzania	Original research	1	1	1	0	0	1	0	0	0	0	0	1	0	0	1	1	Post-conflict
(Sakurai et al., 2016)	Japan	Original research	1	1	0	0	1	0	0	0	1	1	0	1	1	1	0	0	Natural disaster
(Salaniponi, Gausi, Chimzizi, & Harries, 2004)	Malawi	Original research	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	Cross border
(Salari & Kalantari, 2004)	Iran	Original research	0	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0	Post-conflict
(Salvo et al., 2014)	Tibetan diaspora in India	Original research	1	1	0	0	1	0	0	0	0	0	0	1	0	1	0	0	Post-conflict
(Schelling et al., 2005)	Republic of Chad	Original research	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	Remote

(Seddiq, Enarson, Shah, Haq, & Khan, 2014)	Afghanistan	Original research	1	1	1	0	1	1	0	0	1	1	1	1	1	1	1	Post-conflict
(Seita, 2016)	Eastern Mediterranean Region	Conference paper	0	0	0	0	0	0	0	0	1	1	0	1	0	1	0	1	Post-conflict
(Shakoor & Hasan, 2016)	Eastern Mediterranean Region	Conference paper	0	0	1	0	0	1	0	0	0	0	0	0	0	1	0	0	Post-conflict
(Shanks et al., 2012)	Democratic Republic of the Congo	Original research	0	1	0	0	1	0	0	0	0	0	1	1	1	1	0	0	Post-conflict
(Shantha et al., 2012)	Global	Literature review	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	Post-conflict
(Sharaf Eldin et al., 2011)	Sudan	Original research	0	0	1	0	0	0	1	0	0	0	1	1	0	0	0	1	Post-conflict
(M. K. Sharma, Bhatnagar, Goel, Verma, & Swami, 2005)	India	Original research	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	High burden country
(P. R. Sharma et al., 2009)	India	Original research	0	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	Remote
(Shaweno, Shaweno, Trauer, Denholm, & McBryde, 2017)	Ethiopia	Original research	0	0	0	0	1	1	0	1	0	0	0	0	0	1	1	0	Remote
(Shears, 1982)	Somalia	Programme evaluation	1	1	0	0	1	0	0	0	0	1	0	1	0	0	0	0	Post-conflict
(Shears, 1984)	Somalia	Programme report	1	1	0	1	0	0	0	0	0	0	0	1	0	0	0	1	Post-conflict
(Sheik-Mohamed &	sub-Saharan Africa	Literature review	1	1	0	0	1	0	0	0	0	0	0	1	0	1	1	0	Remote

Velema, 1999)																		
(Shimouchi, Kobayashi, Nagata, Urakawa, & Ishkawa, 2015)	Japan	Original research	1	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	Natural disaster
(Singal et al., 2017)	India	Original research	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	Remote
(Soe et al., 2017)	Myanmar	Original research	0	0	0	1	1	0	0	0	0	0	0	0	0	1	1	0	Remote
(Sowa, Nishikura, & Maruki, 1997)	Tibetan diaspora in India and Nepal	Programme report	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	Post-conflict
(Spinaci et al., 1989)	Pakistan	Original research	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	Post-conflict
(Squire, 1997)	Global	Literature review	1	1	0	1	1	1	0	0	1	1	0	1	0	1	1	0	Global (general)
(Stuckler, Steele, Lurie, & Basu, 2013)	Africa	Literature review	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	High burden countries
(Styblo, 1990)	Global	Editorial	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	Global (general)
(Sukrakanchana-Trikham, Puéchal, Rigal, & Rieder, 1992)	Cambodian refugees in Thailand	Original research	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	Post-conflict
(Surenjav et al., 2016)	Mongolia	Original research	0	0	1	0	0	0	0	0	0	1	0	0	0	0	1	0	High burden country
(Sutter & Haefliger,	Vietnam	Original research	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	Post-conflict

1990)																		
(Swaminathan & Narendran, 2008)	India	Literature review	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	High burden country
(Tamas, 2008)	Global	Editorial	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Natural disaster
(Tanser & Wilkinson, 1999)	South Africa	Original research	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	Remote
(Taylor & Zumla, 2000)	Vietnam refugees in Hong Kong camps	Original research	1	1	1	1	1	0	0	0	0	1	0	1	0	0	0	0	Post-conflict
(Tengve, 1968)	Tanzania	Original research	0	1	0	0	0	0	0	1	0	1	0	0	0	0	0	0	Post-conflict
(Thomas, Barrington, Lokuge, & Mercer, 2011)	Papua New Guinea	Original research	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	1	Cross border
(Tigani et al., 2008)	Kosovo	Programme report	0	0	0	0	0	0	0	0	0	0	1	0	1	0	1	0	Post-conflict
(Tiwari & Love, 2007)	Nepal	Original research	0	0	1	1	1	0	1	0	0	0	1	1	1	1	0	0	Conflict
(Tola, Tol, Shojaeizadeh, & Garmaroudi, 2015)	Global	Literature review	1	1	1	1	1	1	0	0	0	0	0	1	0	1	0	0	High burden countries
(Tollefson et al., 2013)	Global	Literature review	0	0	1	0	1	0	0	0	0	0	0	0	0	1	1	0	Indigenous health
(Toscan & Richard, 1988)	Tigrayan refugees to Eastern	Original research	1	1	1	0	1	0	1	0	0	1	1	1	0	0	1	1	Conflict

	Sudan																	
(Trauer, Hajkowicz, Freeman, & Krause, 2011)	Remote Northern Territory	Original research	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	Remote
(Trkanjec, Puljic, & Tekavec, 1994)	Croatia	Commentary	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	Conflict
(Tschampl, Garnick, Zuroweste, Razavi, & Shepard, 2016)	US/Global border	Original research	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	Cross border
(Tschirhart, Nosten, & Foster, 2016)	Thailand-Myanmar border	Original research	0	0	1	0	1	1	0	0	0	1	0	1	0	1	1	1	Post-conflict / Cross border
(Tschirhart, Sein, Nosten, & Foster, 2016)	Thailand-Myanmar border	Original research	0	0	1	0	1	1	0	1	0	0	1	1	0	1	0	1	Post-conflict / Cross border
(Tschirhart, Thi, Swe, Nosten, & Foster, 2017)	Thailand-Myanmar border	Original research	1	0	1	0	1	1	0	0	0	0	0	1	0	1	0	1	Post-conflict / Cross border
(Turpie, 2008)	Somalia	Editorial	1	1	1	0	0	1	0	0	1	1	1	0	1	0	0	0	Conflict
(Uldal et al., 2005)	Russia	Original research	0	0	0	0	0	0	0	1	0	1	0	0	0	1	0	0	Remote
(Ullah, Shah,	Afghanistan	Original research	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	Conflict

Rehman, Kamal, & Begum, 2002)																		/ Remote
(Unger & Riley, 2007)	Global	Literature review	1	0	1	0	0	0	0	0	0	1	1	0	0	0	0	0	High burden countries
(Uttley, 1961)	Antigua	Original research	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	Remote
(van der Oest, Chenhall, Hood, & Kelly, 2005)	New Zealand	Original research	1	0	1	0	1	0	0	0	0	0	0	1	0	1	1	0	Post-conflict / Indigenous health
(Van Der Werf, Hollo, & Noori, 2013)	Eastern Europe	Original research	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	Cross border
(van Lettow et al., 2004)	Malawi	Original research	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	High burden country
(Vieira, Sanha, Riccardi, & Colombatti, 2014)	Guinea-Bissau	Original research	0	0	1	0	0	1	0	0	0	0	1	1	0	0	1	0	Conflict
(Wamai & Larkin, 2011)	Haiti	Commentary	1	0	1	0	0	1	0	0	1	1	0	0	1	1	1	0	Natural disaster
(Wares, Sadutshang, Beeching, & Davies, 2000)	Tibetan diaspora in India	Original research	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	Post-conflict
(Waring et al., 2000)	Indigenous Australia	Original research	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	Remote
(Warsame,	Global	Original research	0	1	0	0	0	1	0	0	0	0	1	0	1	0	1	0	Conflict

Patel, & Checchi, 2014)																		
(Watson, 1982)	Somalia	Programme evaluation	1	1	0	0	1	0	0	0	0	1	1	0	1	1	1	0	Post-conflict
(Wei et al., 2011)	China	Original research	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	Remote
(Weinstock et al., 2001)	Republic of Georgia	Original research	1	1	0	0	0	0	0	0	0	0	1	0	0	0	1	0	Post-conflict
(White, Robinson-White, & Luitel, 1999)	Nepal	Original research	0	0	0	0	0	0	0	1	0	0	0	1	0	1	0	0	Remote
(Williams, 1945)	Britain WW2	Commentary	0	0	0	1	0	0	1	0	0	1	0	0	0	0	1	0	Post-conflict
(Wiysonge et al., 2017)	Global	Systematic review	0	0	1	0	0	0	0	0	0	0	0	1	0	1	1	0	Global (general)
(Wood & Richardson, 2013)	Democratic Republic of the Congo	Commentary	0	1	0	0	0	1	0	0	0	0	1	0	0	0	1	0	Conflict
(Yamasaki-Nakagawa et al., 2001)	Nepal	Original research	0	0	0	1	1	0	0	0	0	0	0	0	0	1	0	0	Remote
(Yang, Liu, & Zhang, 2013)	China	Original research	1	0	1	0	0	0	0	0	0	0	0	1	1	0	0	0	Natural disaster
(Yang, Zhou, & Pan, 2017)	China	Original research	1	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	Natural disaster
(Yao et al., 2011)	China	Original research	0	0	1	1	0	0	0	1	0	1	0	1	0	0	1	0	Remote
(Yoshioka, Morooka, & Kurata, 1958)	Japan	Original research	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Post-war

(Yusuf, 2009)	Pakistan	Programme evaluation	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	High burden country
(Zhang, Liu, Bromley, & Tang, 2007)	Mongolia	Original research	0	0	1	1	1	0	0	0	0	0	0	0	0	1	0	0	Remote
(Zhou, Yang, Zhao, Pan, & Xu, 2016)	China	Original research	0	0	1	1	0	0	0	0	0	0	0	1	0	0	1	0	Natural disaster / Remote
(Zolowere, Manda, Panulo, & Muula, 2008)	Malawi	Original research	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	Remote
GREY LITERATURE																			
(Afghanistan Ministry of Public Health, 2013)	Afghanistan	Strategic Plan	0	0	0	0	1	1	0	1	1	1	1	1	1	1	0	0	High burden country
(Border Health Commission, 2010}	USA-Mexico border	Proceedings report	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	1	Cross border
(Border Health Commission, 2012)	USA-Mexico border	Proceedings report	1	1	1	0	1	1	0	0	0	1	0	1	0	1	1	1	Cross border
(Border Health Commission, 2014)	USA-Mexico border	Proceedings report	0	0	0	0	1	1	0	0	0	0	0	1	0	0	1	1	Cross border
(Brodine, 2010)	USA-Mexico border	Programme report	0	0	0	0	1	1	0	0	0	1	0	1	1	1	1	1	Cross border
(Canada Mortgage and Housing Corporation,	Canada	Government document	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Remote

2004)																		
(Canadian Tuberculosis Committee, 2007)	Canadian Indigenous	Committee statement	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0	Remote
(Carrillo, 2017)	USA-Mexico border	Situation report	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	Cross border
(Doctors of the World, 2004)	Kosovo	Programmatic review	1	0	1	1	1	0	1	0	1	1	1	1	1	1	1	1	Post-conflict
(Goodstein, 2013)	Haiti	Media release	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	Natural disaster
(Medicins sans Frontieres, 2014)	Papua New Guinea	Media release	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	High burden country
(Medicins sans Frontieres, 2015)	Global	Original research	0	0	1	0	1	1	0	0	0	1	0	1	0	1	1	0	High burden countries
(International Union Against Tuberculosis and Lung Disease, 2015)	Global	Committee statement	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	Global (general)
(Lobato, 2000)	USA-Mexico border	Work group report	0	0	0	0	1	0	0	0	0	0	0	1	0	0	1	1	Cross border
(Martins, 2012)	East Timor	Programme report	0	0	0	0	0	1	0	0	1	1	1	1	1	1	1	0	Natural disaster
(Mustafa, 2014)	Kosovo	Programme evaluation	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	Post-conflict
(Noji, 1992)	Global	Guideline	1	1	0	0	0	0	0	0	0	1	0	1	0	1	0	0	Natural disaster
(Norval, 1998)	Cambodia	Programme report	0	1	1	1	1	0	0	0	1	1	1	1	1	0	1	0	Post-conflict
(Ottmani, 2010)	Global	Meeting summary and recommendations	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	Global (general)

(Pan American Health Organization, 2010)	Haiti	Q&A	0	1	0	0	0	0	1	0	1	1	0	1	1	1	0	0	Natural disaster
(Price, 2016)	USA-Mexico border	Legal framework	0	0	0	0	1	0	0	0	0	0	0	1	0	0	1	1	Cross border
(Rieder, 1989)	Global	Position paper	1	1	0	0	0	0	0	0	0	0	0	1	0	0	1	0	Post-conflict
(Swedish Committee for Afghanistan, 2016)	Afghanistan	Situation report	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	Post-conflict
(WHO, 2013)	Global	Guideline	0	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0	Global (general)
(World Health Organization, 1997)	Global	Guideline	1	1	0	1	0	1	0	0	0	0	1	1	1	1	1	1	Post-conflict
World Health Organization, 2001)	Afghanistan	Briefing report	1	0	0	0	1	0	0	0	0	0	0	1	1	0	0	0	Post-conflict
(World Health Organization, 2005)	Global	Guideline	1	1	1	1	1	1	1	1	0	1	0	1	0	1	1	0	High burden countries
(World Health Organization, 2007)	Afghanistan	Country profile	0	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0	High burden country
(World Health Organization, 2012)	Global	Global report	0	0	1	0	1	1	0	0	0	1	0	1	0	0	1	0	Global (general)
(World Health Organization, 2015)	Global	End TB Strategy	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	Global (general)
(World Health Organization,	Russian Federation	Country profile	0	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0	Cross border

2016)																		
(World Health Organization, 2016)	Estonia	Country profile	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	Cross border
(World Health Organization, 2016)	Mexico	Country profile	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	Cross border
(World Health Organization, 2016)	Global	Global report	0	1	1	0	1	1	1	0	0	1	1	1	0	1	1	0	Global (general)
(World Health Organization, 2017)	Global	Global report	1	1	1	0	1	1	0	1	0	1	0	0	0	1	1	0	Global (general)
(World Health Organization, 2018)	Global	Fact sheet	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	Global (general)
(World Health Organization, 2018)	Global	Guideline	0	1	1	0	1	1	0	0	0	1	0	1	0	1	1	0	Global (general)
(World Health Organization, 2018)	Global	Global report	0	1	1	0	1	1	1	1	0	1	0	0	0	1	1	0	Global (general)

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Appendix H2: Scoping Review – What are the common themes when managing TB under challenging circumstances? (December 2017 – December 2022)

Author / Year	Country	Type of Article	Over-crowding (Risk-based) (RB1)	Poor Nutrition (RB2)	Financial constraints (RB3)	Health Illiteracy (RB4)	Treatment Delay (RB5)	Comorbidities (RB6)	Climatic Difficulties (Programmatic Challenges) (PC1)	Geographical Difficulties (PC2)	Damaged Health Infrastructure (PC3)	Limited Human Resources for Health (PC4)	Insecurity (PC5)	Treatment Interruptions (PC6)	Disrupted Health Services (PC7)	Access (PC8)	Allocation of Financial Resources (PC9)	Cross Border (PC10)	Setting
Aboukheir et al., (2019)	Puerto Rico	Editorial	0	0	0	0	1	0	0	0	1	1	0	1	1	1	0	0	Natural disaster
Alvarez et al., (2020)	Canada	Original research	0	0	0	0	0	0	1	1	0	1	0	1	1	1	0	0	Remote / Indigenous health
Alvarez et al., (2021)	Canada	Original research	1	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	Remote / Indigenous health
André et al., (2018)	West Africa	Original research	1	0	1	0	1	0	0	0	0	1	0	0	0	1	1	0	High burden countries
Bahrainwala et al., (2020)	East Africa	Original research	0	0	1	0	0	0	0	1	0	1	0	1	0	1	1	0	Remote / High burden countries /
Bhat et al. (2022)	India	Original research	0	0	1	1	1	0	0	1	0	1	0	0	0	1	0	0	Remote / High burden countries
Bionghi et al. (2018)	South Africa	Original research	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	Remote
Bowerman (2020)	Alaska (USA)	Literature review	0	0	0	0	1	0	1	1	0	0	0	1	1	1	0	0	Remote / Indigenous health
Byonaneby e et al. (2021)	East Africa	Original research	0	0	0	1	0	1	0	0	0	1	0	1	0	1	0	0	High burden countries
Charles et	Haiti	Original	0	0	0	0	0	0	1	0	1	1	0	1	1	1	0	0	Natural

al. (2021)		research																disaster
Deribew et al. (2020)	Horn of Africa	Original research	0	0	0	1	0	1	0	1	0	1	0	0	0	1	0	0	High burden countries
Diefenbach-Elstob et al. (2019)	Papua New Guinea	Original research	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	Remote / High burden countries
Eyo et al. (2021)	West Africa	Original research	0	0	1	1	0	0	0	1	0	1	0	0	0	1	0	0	High burden countries
Fatima et al. (2021)	Pakistan	Original research	0	0	0	1	1	0	0	0	0	0	0	1	1	1	0	0	High burden countries
Foster et al. (2021)	Australia	Original research	0	0	0	0	1	0	1	1	0	0	0	0	0	1	0	1	Remote / Indigenous health
Galgallo et al. (2020)	East Africa	Original research	0	1	0	0	0	0	0	0	0	0	0	1	0	1	1	0	High burden countries
Gleerup & Vedsted (2022)	Greenland	Original research	0	0	0	0	1	0	1	1	0	0	0	0	0	1	0	0	Remote / High burden countries
Haldane et al. (2021)	China	Original research	0	0	1	1	1	0	1	1	0	1	0	1	1	1	0	0	Remote
Jain et al (2020)	India	Literature review	0	1	0	0	0	1	0	0	0	0	0	1	1	1	1	0	High burden countries
Jiang et al. (2019)	China	Original research	0	0	1	0	0	0	0	1	0	0	0	1	0	1	1	0	High burden countries
Jones et al. (2019)	Solomon Islands	Original research	0	0	0	0	1	0	0	1	0	1	0	1	0	0	1	0	High burden countries
Kilabuk et al. (2019)	Canada	Original research	1	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	Remote

Author / Year	Country	Type of Article	Over-crowding (Risk-based) (RB1)	Poor Nutrition (RB2)	Financial constraints (RB3)	Health Illiteracy (RB4)	Treatment Delay (RB5)	Comorbidities (RB6)	Climatic Difficulties (Programmatic Challenges) (PC1)	Geographical Difficulties (PC2)	Damaged Health Infrastructure (PC3)	Limited Human Resources for Health (PC4)	Insecurity (PC5)	Treatment Interruptions (PC6)	Disrupted Health Services (PC7)	Access (PC8)	Allocation of Financial Resources (PC9)	Cross Border (PC10)	Setting
Kuupiel et al. (2019)	West Africa	Original research	0	0	0	0	1	0	0	1	0	0	0	0	0	1	0	0	High burden countries
Ma et al. (2021)	China	Original research	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	High burden countries
Malacarne et al. (2019)	Brazil	Original research	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	High burden countries
Mesic et al. (2020)	Afghanistan	Original research	0	0	0	0	1	0	0	0	0	0	1	0	0	1	0	0	High burden countries
Miller et al. (2020)	Australia	Editorial	0	0	0	1	1	0	0	1	0	0	0	0	0	0	0	0	Remote / Indigenous health
Moyo et al. (2021)	East Africa	Original research	1	0	0	0	0	1	0	0	0	0	0	1	0	1	0	0	High burden countries
Muller et sl. (2022)	East Africa	Original research	0	1	1	0	1	1	0	0	0	1	0	1	0	1	1	0	High burden countries
Murray et al. (2019)	Philippines	Original research	1	0	0	0	1	0	0	1	0	0	0	1	1	1	0	0	Natural disaster
Nouvet et al. (2019)	East Africa	Original research	0	1	0	1	0	0	0	1	0	1	0	0	0	0	1	0	High burden countries
Pease et al. (2021)	Canada	Original research	0	0	0	0	0	0	1	1	0	0	0	0	0	0	1	0	Remote / Indigenous health
Pease et al. (2019b)	Canada	Original research	0	0	0	0	0	0	1	1	0	0	0	1	0	1	0	0	Remote / Indigenous health
Reeves et al. (2020)	East Africa	Original research	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	High burden countries
Sadananda et al.	East Africa	Original research	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	High burden

(2020)																		countries
Simbwa et al. (2021)	East Africa	Original research	1	1	1	0	0	0	0	1	0	0	0	1	1	1	0	0	High burden countries
Souza et al. (2021)	Brazil	Original research	1	0	1	0	0	0	0	0	0	0	0	1	0	1	0	0	High burden countries
Thomas et al. (2021)	India	Original research	1	0	1	0	0	0	0	1	0	0	0	1	1	0	0	0	High burden countries
Timire et al. (2019)	East Africa	Original research	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	High burden countries
Ullah et al. (2020)	Pakistan	Original research	0	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	High burden countries
Vyas et al. (2019)	India	Original research	0	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	High burden countries
Wang et al. (2021)	China	Original research	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	High burden countries
Wei et al. (2019)	Tibet	Original research	0	0	1	1	0	0	1	1	0	1	0	1	0	0	0	0	High burden countries

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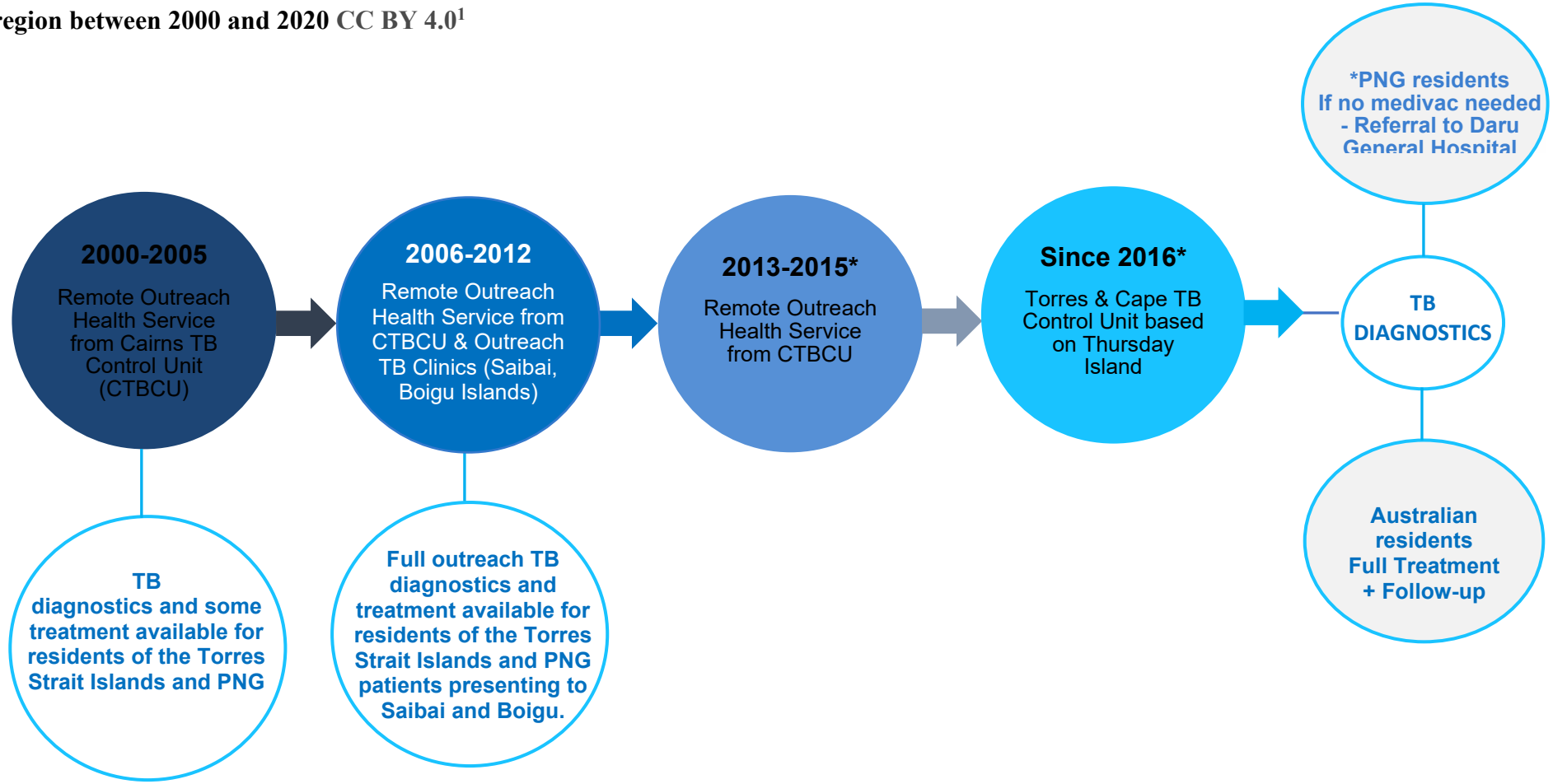
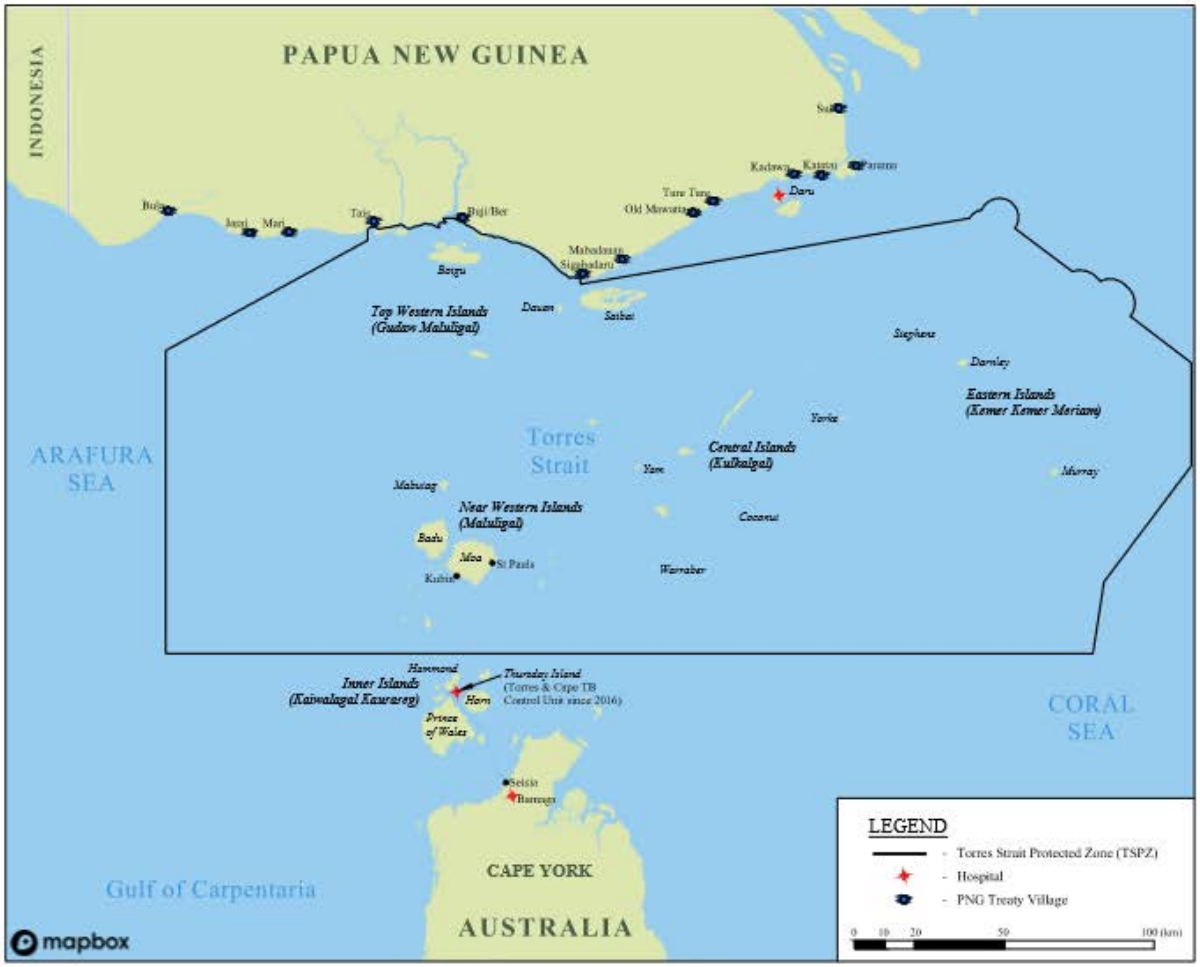
Appendix I: Other Research Output

Appendix I1: Description of the different tuberculosis programmatic time periods in the Torres Strait / Papua New Guinea cross-border region between 2000 and 2020 [1]



[1] DOI. 10.6084/m9.figshare.16834648

Appendix I2: Torres Strait and PNG Map



Appendix I3: Variables of datasets created for this thesis – Management of TB in the Torres Strait including PNG nationals that presented to health facilities in the Torres Strait Protected Zone (TSPZ) between 2000 and 2020

Dataset A	**Dataset B**	**Dataset C**	**Dataset D**
All laboratory-confirmed pulmonary TB cases diagnosed between January 2000 and March 2020 where at least three sputum specimens were collected	**All drug-resistant TB cases diagnosed in the Torres Strait between January 2000 and March 2020**	**All PNG national patients that entered Australia via the TSPZ and presented with presumptive TB between January 2016 and December 2019**	**All PNG national paediatric patients (<15 years) that entered Australia via the TSPZ and presented with presumptive TB between January 2016 and December 2019**
Age	Age	Age	Age
Age group	Age group	Age group	Age group
Gender	Gender	Gender	Gender
Indigenous status	Indigenous status	Location of residence	Location of residence
Visa status	Visa status	Visa status	Treaty status
Location of residence	Country of birth	Primary Health Centre (PHC) the patient presented to	PHC the patient presented to
Treaty status	PHC patient presented to	Queensland Adult Deterioration Detection Score (Q-ADDS)/Child Early Warning Tool (CEWT)/Queensland Maternity Early Warning Tool (Q-MEWT) scores	Month of presentation
Human Immunodeficiency Virus (HIV) status	Location of residence	Medivac history	Year of presentation
Cavitary disease on chest x-ray	Onset of symptoms to presentation at a health facility (days)	Hospital that the patient was medically evacuated to	Weight
Miliary disease on chest x-ray	Presentation at a health facility to diagnosis (days)	Length of stay in hospital	Age / weight percentile
Disease type	Diagnosis to treatment commencement (days)	Disease type	Laboratory-confirmed TB diagnosis
Disease site	Total number of days from onset of symptoms to treatment commencement	Disease site	Clinical TB diagnosis
Drug susceptibility testing	Patient outcome	Patient outcome (died/survived; discharged/transfer out; arrived at	Disease site

		Daru/loss to follow up)	
Year diagnosed	Treatment group	Vital signs	Drug susceptibility testing
Month diagnosed	Xpert diagnosis	Weight	Cough
Specimen quality	AFB positivity	Age / weight percentiles	Fever
Specimen modality	Culture confirmation		Loss of weight
Specimen packaging errors	Treaty status		Night sweats
Specimen transport errors	Diagnosis in Top Western Cluster		Haemoptysis
Specimen documentation errors	Case type		Enlarged lymph nodes
Diagnostic yield	HIV status		Close contact status
Acid-fast bacilli (AFB) positivity	Cavitary disease		Chest x-ray results
	Close contact		Microbiological results
	Comorbidities		Bacille Calmette-Guerin status
	Cough		Duration of illness
	Fever		Abdominal swelling
	Weight loss		Spine deformity
	Night sweats		Slow neurological signs
	Haemoptysis		Joint swelling
	Isoniazid resistance		
	Rifampicin resistance		
	Streptomycin resistance		
	Ethionamide resistance		
	Multidrug-resistance (MDR)		
	Ethionamide resistance with MDR		
	Haemoglobin z score		
	Lymphocyte z score		
	Albumin z score		
	Year of diagnosis		
	Year group		
	Disease site		
	Disease type		
	AFB positivity		

Appendix J: Queensland Health

Appendix J1: Queensland Notifiable Conditions [1] included in the Cross Border Data Integrity Project

A	Acute flaccid paralysis (AFP) Acute post-streptococcal glomerulonephritis Acute rheumatic fever Acute viral hepatitis Adverse events following immunisation Amoebic Meningoencephalitis Anthrax Arbovirus infections Australian bat lyssavirus Avian influenza	M	Malaria Measles Melioidosis Meningitis (all types) Meningitis (viral) Meningococcal disease Middle East Respiratory Syndrome Coronavirus (MERS CoV) MRSA Mumps Murray Valley encephalitis
B	Barmah Forest virus (arbovirus infection) Botulism Brucellosis	N	Non-tuberculous (atypical) mycobacterial infections Norovirus Novel coronavirus
C	Campylobacter enteritis Chancroid Chickenpox Chikungunya virus	P	Pandemic influenza Paratyphoid Parvovirus B19 Pertussis Plague

	Chlamydia trachomatis Cholera Ciguatera poisoning Creutzfeldt–Jakob disease Cryptococcosis Cryptosporidiosis Cytomegalovirus		Pneumococcal Disease (invasive) Poliomyelitis Post-streptococcal (acute) glomerulonephritis Primary Amoebic Meningoencephalitis (PAM) Psittacosis
D	Dengue Diarrhoea in young children Diphtheria Donovanosis	Q	Q Fever
E	Ebola Echinococcosis Enterohaemorrhagic Escherichia coli infection (EHEC) Enterovirus 71 (EV71) neurological disease	R	Rabies Rheumatic fever (acute) Rheumatic heart disease Ringworm Ross River virus Rotavirus Rubella
F	Flavivirus (unspecified) Foodborne illness (suspected)	S	Salmonella infection Scabies Severe acute respiratory syndrome (SARS) Shiga toxin-producing Eschericia coli infection (STEC)

			Shigella infection Shingles Smallpox Staphylococcus aureus infection Streptococcal Disease - Invasive Group A Syphilis
G	Gastroenteritis Genital herpes Genital warts German measles Gonorrhoea Granuloma inguinale Group A Streptococcal Disease	T	Tetanus Tinea Toxocariasis Toxoplasmosis Trachoma – eye infection Tuberculosis Tularaemia Typhoid and paratyphoid
H	Haemolytic uraemic syndrome (HUS) Haemophilus influenzae type B (Hib) Hand, foot and mouth disease Hansen's disease Head lice Hendra virus Hepatitis A Hepatitis B Hepatitis C Hepatitis D	V	Vaccination - adverse events following immunisation Varicella-zoster infection Vibrio vulnificus infection Viral haemorrhagic fever

	Hepatitis E Histoplasmosis Human immunodeficiency virus (HIV) infection Hydatid disease		
I	Influenza (the flu) Invasive Group A Streptococcal Disease Invasive pneumococcal disease	W	Water-borne or food-borne illness in 2 or more related cases Whooping cough
J	Japanese encephalitis	Y	Yellow fever Yersiniosis
K	Kunjin virus	Z	Zika virus
L	Lead exposure Legionellosis Leprosy Leptospirosis Listeriosis Lymphogranuloma venereum (LGV) Lyssavirus (Australian bat)		

Reference:

Queensland Health. *Communicable disease control guidance.* 2016: Brisbane, Queensland.

The following policies and procedures were retracted from this thesis post-examination as requested by the Torres and Cape Hospital and Health Service Chief Executive, Ms. Beverley Hamerton, on 17 February, 2023.

Appendix J2: Management of Papua New Guinea Nationals accessing healthcare within the Australian Islands of the Torres Strait Protected Zone, presumed to have or diagnosed with Tuberculosis

Appendix J3: Initial Visit forms used in the Torres and Cape Hospital and Health Service for residents of Papua New Guinea nationals

Appendix J4: TB Screening – PNG National Escort Algorithm

Appendix J5: TB Screening – PNG National Patients Requiring Medevac Algorithm

Appendix J6: Papua New Guinea Traditional Inhabitants Presenting to Queensland Health Facilities within the Australian Islands of the Torres Strait Protected Zone

Appendix J7: Management of Papua New Guinea Traditional Inhabitants Presenting to Queensland Health Facilities within the Australian islands of the Torres Strait Protected Zone

Appendix J8: PNG Procedure Flowchart

Appendix J9: Management of patients with suspected or confirmed pulmonary tuberculosis throughout TCHHS

Appendix J10: Initial Visit and Contact Tracing Form Used in the Torres and Cape Hospital and Health Service for Residents of the Torres Strait and Cape Communities