Predictors of poor outcome in patients diagnosed with drug-resistant tuberculosis in the Torres Strait / Papua New Guinea border region

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NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
ABSTRACT

Drug-resistant tuberculosis (DR-TB) is an ongoing challenge in the Torres Strait / Papua New Guinea border region. Treatment success rates have historically been poor for patients diagnosed with DR-TB, leading to increased transmission and resistance multiplication risk. This study aimed to identify predictors of poor 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. Univariate and multivariate predictors of poor outcome were analysed. Poor outcome was defined as treatment default, treatment failure and death (versus cure or completion).

In total, 133 patients with resistance to at least one TB drug was 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. Poor 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 poor outcome ($p < 0.05$), but numbers were very small. Among all 133 DR-TB patients, 41% had a low lymphocyte count, which was significantly associated with poor outcome ($p < 0.05$). Overall, outcome improved in recent years with a 50% increase in the chance of a good outcome per year group over the study period; on binary logistic regression analysis. Being a close contact of a known TB case was associated with improved outcome.

While DR-TB treatment outcomes have improved over time, it remains important to prevent DR-TB spread and resistance multiplication resulting from suboptimal treatment. Enhanced surveillance for DR-TB, better cross border collaboration and consistent diagnosis and management of comorbidities and other risk factors should further improve patient care and outcomes.
Introduction:

Drug resistance is a significant threat to control of tuberculosis (TB), 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 (FS)-TB, any of the second-line drugs used to treat DR-TB, or are resistant to a combination of these drugs (2). Non-compliance or inadequate FS-TB treatment regimens may lead to the development of DR-TB and multidrug-resistant (MDR)-TB – that which is resistant to both isoniazid and rifampicin - which is substantially more difficult and costly to treat (3). Treatment outcomes are generally worse for DR-TB cases due to prolonged treatment regimens and severe adverse effects of TB drugs (4). Globally, the average treatment success rate in patients with MDR-TB is reported to be 50% (5) however this varies across countries (Ukraine – 18.1% (6); China – 52.2% (7); Ethiopia – 78.6%) (8).

TB is an ongoing threat in the Torres Strait / Papua New Guinea (PNG) region which is compounded by high levels of DR-TB in the Western Province of PNG and in particular, on Daru Island (9, 10) (Fig 1). The conservative incidence rate of TB in PNG is 432 / 100,000 population (WHO, 11) and 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% identify as Torres Strait Islander (14), and Indigenous Australians are disproportionately affected by TB when compared to non-Indigenous Australians (15). Significantly, residents from specific islands in the Torres Strait and villages in the Western Province of PNG share an open international border (Fig 1), heightening TB transmission risk in the region (10).
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

Fig 1. Map of the Torres Strait / Papua New Guinea cross-border region (16) CC BY 4.0

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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
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 coinfection / comorbidities such as renal impairment, diabetes and HIV are more likely to have poor outcomes (18-20). Many studies have reported high rates of mortality in TB patients with comorbidities (21-24) and in patients with low levels of haemoglobin, albumin and lymphocytes (25).

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 targets of the WHO to End TB, aiming to reduce the incidence of TB by 90% before 2035 (26).

Little is known about predictors of treatment outcomes in patients diagnosed with DR-TB in the Torres Strait / PNG border region. The aim of this study was to evaluate the association of comorbidities / coinfection, the levels of a suite of serum biomarkers 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
This is a retrospective cohort study of 133 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 mono, poly and multidrug-resistant TB.

All residents of the Torres Strait Islands and residents of the PNG villages adjacent to the northern Australia / PNG border who were diagnosed in the Torres Strait with laboratory-confirmed DR-TB
were included in the study. 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 over different time periods between 2000 to 2020 (2000-2005; 2006-2012; 2013-2015; 2016-2020). Across all models of TB care, the primary mode of diagnosis was via sputum collection and the collection of specimens for the diagnosis of extrapulmonary TB was rarely available in remote Australian border clinics. Isolation of mycobacterial culture, drug susceptibility testing and genotyping for specimens collected in this region were performed in the Queensland Mycobacterium Reference Laboratory in Brisbane (Fig1). (27). The major differences in care resulting from these changes were reduction in time to treatment commencement and retention in care (28).

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 (29). 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 service coverage capability in PNG (30), thus 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 of rapid response to suspected and confirmed case notifications occurred from 2016 and is ongoing (31). All Australian residents in this study were managed within the Australian healthcare system.
Data Collection

Queensland Health’s Notifiable Conditions System (NoCS) was used to source case notification data. Only cases with laboratory confirmed drug-resistant TB were included in the study, including those resistant to streptomycin. One case was added to the study where their drug-resistant status was identified in Queensland Health’s laboratory software, AUSLAB but was not registered as a drug-resistant TB case in NoCS.

Raw data pertaining to biomarkers (haemoglobin, albumin, lymphocyte levels) were obtained from Queensland’s laboratory results software, AUSLAB. These biomarkers are routinely collected in most patients presenting to primary healthcare facilities in the Torres Strait.

Definitions

Treatment outcome definitions used in the study were as per Laserson et al. (32). Poor treatment outcome was defined as death, default or treatment failure. Good treatment outcome was defined as completed treatment or cured. Other treatment outcome was defined as transfer out, to indicate that the patient had been referred back to the PNG health system. In some patients that were transferred out, treatment outcome was unknown.

Comorbidities / coinfection were defined as HIV, diabetes and renal impairment. In patients with comorbidities recorded as renal dysfunction, renal insufficiency, renal disease and renal failure were all defined as having renal impairment.

Site of disease included pulmonary TB, extrapulmonary TB or both. Case type refers to either newly diagnosed TB cases as well as those who had previously received full or partial treatment.

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 (Fig 2), site of disease, case type, comorbidities/coinfection, 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 poor treatment outcomes.

Potential categorical predictors (site of disease, HIV serology, case type, comorbidities/coinfection, drug resistance and selected biomarkers including haemoglobin, lymphocytes and albumin), were analysed by poor, good 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, which when compared to Pearson’s Chi-squared test are more likely to be Exact, were undertaken to ascertain association with poor treatment outcome for variables with 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.

Pearson’s Chi-squared tests were performed to assess whether selected biomarkers (haemoglobin, lymphocyte and albumin levels) were associated with binary treatment outcomes (poor or other). Multiple imputation was not used for these analyses and numbers of patients that had biomarkers available were reported. 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 (poor 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 (2016, North Ryde, Australia). 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. Similarly, low albumin and lymphocyte levels were defined as those
with a Z score at least 2SD away from the mean.

Univariate analysis of comorbidities/coinfection, diagnosis year group, contact with a known case,
biomarkers, acid-fast bacilli (AFB) positivity and rifampicin-resistance were examined as potential
predictors of poor 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)
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:**

Of the 133 patients with DR-TB there were 22 deaths and one failed therapy, 16 defaulted and 51
were transferred out. Of the 51 that were transferred out, 41 had no known outcome. As shown in
Table 1, Boigu Island PHC received fewer patients than Saibai Island PHC but had greater treatment
success (49% vs 38%). The median age was 28, and patients in the 15-29 years age group were both
the largest group and disproportionately affected by poor outcomes (Table 1). Eighty-three percent
of older adults aged ≥60 years had a poor outcome, and of those >61 years, 100% died. There was no
effect of sex on outcome. Being a PNG national rather than an Australian Torres Strait Islander was
highly predictive of poor outcome.
Table 1. Demographic characteristics of all patients diagnosed with drug-resistant tuberculosis in the Torres Strait Islands between 2000 and 2020, and their association with good, poor and other TB treatment outcomes

| Characteristic                        | Treatment Outcomes N = 133 (%) | P      |
|--------------------------------------|--------------------------------|--------|
|                                      | Good                           | Poor   | Other  |        |
|                                      | Cured | Completed | Died | Failed | Defaulted | Transfer Out | Total |
| Age group                            |       |           |      |        |           |            |       |
| <5 years                             | 2 (22)| 5 (56)    | 0 (0)| 0 (0)  | 0 (0)     | 2 (22)       | 9 (9) |
| 5-14 years                           | 1 (10)| 3 (30)    | 1 (10) | 0 (0)  | 2 (20)   | 3 (30)       | 10 (9) |
| 15-29 years                          | 3 (5) | 21 (34)   | 10 (16)| 0 (0)  | 10 (16)  | 18 (29)      | 62 (47) |
| 30-44 years                          | 6 (18)| 9 (27)    | 5 (15)| 0 (0)  | 4 (12)   | 9 (27)       | 33 (25) |
| 45-59 years                          | 0 (0) | 2 (15)    | 2 (15)| 0 (0)  | 0 (0)    | 9 (70)       | 13 (10) |
| ≥ 60 years                           | 1 (17)| 0 (0)     | 4 (67)| 1 (17)| 0 (0)    | 0 (0)        | 6 (4)  |
| Gender                               |       |           |      |        |           |            |       |
| Female                               | 9 (12)| 22 (30)   | 14 (19)| 1 (1)  | 8 (11)   | 21 (28)      | 75 (56) |
| Male                                 | 4 (7) | 18 (31)   | 8 (14)| 0 (0)  | 8 (14)   | 20 (35)      | 58 (44) |
| Country of Birth                     |       |           |      |        |           |            |       |
| Australia                            | 3 (50)| 2 (33)    | 1 (17)| 0 (0)  | 0 (0)    | 0 (0)        | 6 (4)  |
| Papua New Guinea                     | 10 (8)| 38 (30)   | 21 (17)| 1 (1)  | 16 (13)  | 41 (32)      | '127 (95) |
| Visa Status                          |       |           |      |        |           |            |       |
| Australian resident                  | 3 (33)| 3 (33)    | 2 (22)| 1 (11)| 0 (0)    | 0 (0)        | 9 (6)  |
| Papua New Guinea Treaty Visitor      | 5 (6) | 23 (27)   | 15 (17)| 0 (0) | 13 (15)  | 30 (35)      | 86 (62) |
| Papua New Guinea non-Treaty Visitor  | 5 (13)| 14 (37)   | 5 (13)| 0 (0)  | 3 (8)    | 11 (29)      | 38 (28) |
| Primary Health Centre Attended       |       |           |      |        |           |            |       |
| Saibai Island                        | 11 (10)| 32 (29)  | 19 (17)| 1 (1)  | 14 (13)  | 33 (30)      | 110 (83) |
| Boigu Island                         | 2 (13)| 7 (44)    | 2 (13)| 0 (0)  | 2 (13)   | 3 (19)       | 16 (12) |
| Murray Island                        | 0 (0) | 0 (0)     | 0 (0) | 0 (0)  | 0 (0)    | 2 (100)      | 2 (1)  |
| Darnley Island                       | 0 (0) | 1 (50)    | 0 (0) | 0 (0)  | 0 (0)    | 1 (50)       | 2 (1)  |
| Yorke Island                         | 0 (0) | 0 (0)     | 1 (50)| 0 (0)  | 0 (0)    | 1 (50)       | 2 (1)  |
| Thursday Island                      | 0 (0) | 0 (0)     | 0 (0) | 0 (0)  | 0 (0)    | 1 (100)      | 1 (1)  |

† Percentages may not equal 100 due to rounding.
Table 2 shows that DR-TB patients diagnosed between 2000 and 2005 were more likely to have poor outcomes (50%) than those diagnosed between 2016 and 2020 (17%). Of 133 cases of DR-TB, 67% had MDR-TB and of those, 74% (n = 66) were new cases and 32% had a poor outcome. Ethionamide resistance was only identified in patients diagnosed with MDR-TB (p <.001) and 90% of MDR-TB cases were ethionamide resistant. Nearly one in five patients had previously received full or partial treatment in Australia or PNG. The composite variable for comorbidities/coinfection were comprised of four DR-TB / HIV coinfection cases, three DR-TB / diabetes comorbidity cases and four DR-TB / renal comorbidity cases. Seventy-five percent of patients with DR-TB/HIV coinfection died, and 100% of patients with DR-TB/diabetes comorbidity died. Overall, 78% of patients with DR-TB and at least one coinfection/comorbidity had a poor outcome.

Table 2. Clinical variables of patients diagnosed with drug-resistant tuberculosis in the Torres Strait between 2000 and 2020, and their association with good, poor and other TB treatment outcome

| Variable                           | Treatment Outcome N = 133 (% of total) |   |   |   |
|------------------------------------|---------------------------------------|---|---|---|
|                                    | Poor (N = 39; 29%) | Good (N = 53; 40%) | Other (N = 41; 31%) | Total |
| Diagnosis Year Group*              | 133 | .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 | .08 |
| Pulmonary TB                       | 25 (34) | 22 (30) | 26 (36) | 73 |
| Extrapulmonary TB                  | 2 (20) | 7 (50) | 1 (10) | 10 |
| Both PTB and XPTB                  | 12 (24) | 24 (48) | 14 (28) | 50 |
| Case Type                          | 133 | .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 / Coinfection        | 133 | .003 |
| Diabetes Mellitus, Renal Disease or HIV | 7 (78) | 0 | 2 (22) | 9 |
| No known risk factors              | 32 (26) | 53 (43) | 39 (32) | 124 |
| Drug Resistance                | 133 | .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 | .8 |
| Ethionamide resistant          | 24 (30) | 30 (38) | 26 (33) | 80 |
| Susceptible                   | 15 (28) | 23 (43) | 15 (28) | 53 |
| Cough                         | 114 | .1 |
| Cough                         | 27 (31) | 31 (36) | 29 (33) | 87 |
| No cough                      | 4 (15) | 15 (56) | 8 (30) | 27 |
| Close Contact                 | 133 | .02 |
| Close contact                 | 8 (16) | 23 (45) | 20 (39) | 51 |
| No known contact              | 31 (38) | 30 (37) | 21 (26) | 82 |

Note. poor outcome - died, failed, defaulted; good 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.

#Close contact to a known TB case as reported by patient.

PTB, pulmonary TB; XPTB, extrapulmonary TB; MDR-TB, multidrug-resistant TB.

Table 3 shows that 86% of patients with haemoglobin recorded had anaemia, and of those, 38% had severe anaemia. Low albumin was detected in 76% of patients that had levels recorded. In patients with low lymphocyte levels, 44% of patients had a poor outcome.

Table 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 (%) | Poor | Other | Total | P   |
|---------------------------|-------------------------|------|-------|-------|-----|
| **Haemoglobin Levels** (50-146L) | 107 | .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 | .01 |
| Normal                    | 13 (21) | 50 (79) | 63 |
| Low                       | 19 (44) | 24 (56) | 43 |
| **Albumin** (<15-48L)     | 105 | .07 |
*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.

In Table 4, patients with comorbidities / coinfection, low lymphocyte levels and AFB positivity were significantly more likely to have poor outcomes. Being a close contact of a known TB case was a protective factor and reduced the odds of a poor outcome occurring (p < 0.008; OR < 0.31). Although the p value for anaemia in Table 3 was > 0.1, this variable was included in the univariate analysis as other studies have demonstrated an association between anaemia and poor outcomes (33), however in this study, anaemia was not a significant predictor of poor outcomes. In the adjusted multivariate model, comorbidities / coinfection, being a close contact of a known TB case and low lymphocyte levels retained significance (p < 0.05).

Table 4. Predictors of poor treatment outcome among drug-resistant tuberculosis cases diagnosed in the Torres Strait / Papua New Guinea border region between 2000 and 2020 (n = 133)

| Variable                              | Univariate Analysis | Multivariate Analysis |
|---------------------------------------|---------------------|-----------------------|
|                                       | N (%)               | OR (95% CI)           | p-value   | aOR (95% CI)       | p-value   |
| Comorbidities / Coinfection (DM, renal, HIV) | 9 (7)               | 10.06 (1.98-50.96)    | < 0.005   | 17.4 (2.6-117.06)  | < 0.003   |
| Contact with known TB case            | 51 (38)             | 31 (.12-.73)          | < 0.008   | 3 (.08-.87)        | < 0.03    |
| Low lymphocyte level                  | 43 (32)             | 3.05 (1.29-7.17)      | < 0.01    | 2.7 (1.1-7.08)     | < 0.04    |
| AFB positive                          | 80 (60)             | 2.4 (1.07-5.58)       | < 0.03    | 1.6 (.56-4.48)     | < 0.4     |
| Rifampicin resistance                 | 93 (70)             | 2.5 (.96-6.21)        | < 0.05    | Eliminated at forward step |
| Anaemia                               | 93 (70)             | 1.9 (.50-7.26)        | < 0.3     | Eliminated at forward step |
| Low albumin level                     | 80 (60)             | 2.8 (.88-9.05)        | < 0.08    | Eliminated at forward step |
| Female sex                            | 75 (56)             | 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.

Discussion:
This is the first study, to the best of our knowledge, to identify predictors of poor treatment outcomes in patients diagnosed with DR-TB and examine the impact of four different models of TB care over two decades in the Torres Strait / PNG border region. We found a 50% improvement in good treatment outcomes under the model of care involving a local TB unit from 2016 compared with earlier models. Patients diagnosed before 2013 were significantly more likely to have poor treatment outcomes in this study and this 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 drugs was only available for PNG nationals in this study 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.

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 initiatives are consistent with the Australian National Tuberculosis Advisory Committee recommendations to engage in regional and bilateral collaborations in order to improve TB services in high-risk areas (37).
This study also found that close contacts of previous TB cases were afforded a protective factor against poor treatment outcomes. 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 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 both isoniazid and rifampicin resistance may be more likely to remain infectious longer than patients with DS-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 linking in with healthcare services earlier, perhaps while accompanying previously diagnosed household members to clinic appointments. 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).

A limitation in this study is that it 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/coinfection.
Another potential limitation of this study is that only people with TB isolates with at least one frontline drug resistance was included. Hence the full impact of MDR treatment (compared with fully susceptible TB) could not be evaluated. We were however able to compare those with and without rifampicin resistance, finding a trend to worse outcome.

Patients with pre-existing comorbidities/coinfection in this study were significantly more likely to have poor treatment outcomes. This finding is consistent with that of other studies that report worse treatment outcomes for patients with comorbidities/coinfection (6, 41, 42). In our study, no patients with a reported comorbidity/coinfection were cured or completed treatment. One hundred percent of patients with DR-TB/diabetes comorbidity died and 75% of patients with TB/HIV coinfection had a poor outcome, and this is cause for concern. While HIV is a very strong predictor for the development of active TB disease, HIV is unlikely to be a major contributing factor in TB transmission dynamics in the region as currently less than 1% of the population is infected (43). Regardless, the high proportion of poor treatment outcomes in patients with TB/HIV coinfection suggests routine HIV testing is warranted for all patients diagnosed with TB in this setting. It is also possible that ‘stand-alone’ or vertical disease programs of TB control, diabetes management and sexual health in the current health system may contribute to poor outcomes for coinfected patients (44). To help mitigate poor outcomes in patients with DR-TB/diabetes and DR-TB/HIV coinfection, it may be beneficial for TB programs to establish linkages with both diabetes educators and sexual health providers to provide enhanced screening, monitoring and management of patients with these comorbidities / coinfection (45). 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.

Aboriginal and Torres Strait Islander peoples develop chronic kidney disease three times as often as non-Indigenous Australians (46) and in Torres Strait Islander adults, a recent survey found that nearly one in five people showed signs and symptoms of chronic kidney disease (47). In renal
patients, delayed diagnosis of TB is a possible reason for poor prognosis (24). 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 (24). Early detection of TB in renal patients may be key to improved outcomes (24). Efforts to increase collaboration between renal and TB units in the Torres Strait may help reduce diagnostic delay and better support shared patients.

In this study, we also evaluated low serum haemoglobin, albumin and lymphocyte levels as predictors of poor outcomes of DR-TB. Our findings show that low lymphocyte levels are statistically significantly associated with poor treatment outcomes in DR-TB patients, consistent with other studies (48). In patients that have had TB for sustained periods such as those with previous treatment default or failure, overall health decline evidenced by low lymphocyte levels can be a marker for severity of TB disease which can be more complex to manage (49). When compared to FS-TB, lower lymphocyte counts have been reported in MDR-TB patients (50). Low lymphocyte levels, AFB positivity, and skewed distribution of low haemoglobin and low albumin levels in DR-TB cases, are all representative of poor health at diagnostic baseline, as were observed in this study.

In other studies, serum haemoglobin and albumin were strong predictors of mortality (51) and in China and Israel, an association between hypoalbuminaemia and poor prognosis in DR-TB patients has been reported (7, 52). Further, a study conducted in Ethiopia reported that MDR-TB patients with low haemoglobin levels (anaemia) were more than twice as likely to have poor treatment outcomes when compared to patients without anaemia (41). Although anaemia and hypoalbuminaemia were not statistically significantly associated with poor outcomes for DR-TB patients in this study, it is unlikely that this was due to clinical manifestations of disease and more likely a power issue as nearly all patients in this study were anaemic and hypoalbuminaemic. Low haemoglobin has been associated with poor outcomes in TB patients, as well as delayed sputum conversion at two months (53). This may help to explain the significant association in this study.
between poor outcomes and patients with AFB positive DR-TB, although this study did not examine timing of sputum conversion. It is possible that the cause of anaemia in DR-TB patients is due to iron nutritional deficiency (33), however this study did not explore levels of iron, ferritin, hepcidin and transferrin.

Limitations

Our study has several limitations, some of which have been described above. Additionally, this study only included DR-TB patients which may have impacted the power of statistical analyses. Future studies could incorporate drug-susceptible patients in the same periods to use as a 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.

Conclusion

Although having a locally-based TB program in the Torres Strait has resulted in better treatment outcomes for DR-TB patients, interventions to both reduce the likelihood of poor outcomes and refine the focus on maximising treatment completion in vulnerable sub-population groups at risk of poor outcomes are needed. Comorbidities and poor health indicators at diagnosis show that DR-TB is occurring in vulnerable populations. These findings have important implications for TB programs on both sides of this international border where DR-TB is prevalent, and there are multiple operational modifications worth consideration. Routine incorporation of key strategies should include collaborative working relationships with diabetes/renal/sexual health care providers to consistently identify and manage TB in patients with comorbidities, enhanced cross border collaboration and ongoing commitment to point of care HIV and baseline blood testing that may help to flag DR-TB patients at-risk of poor outcomes.
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