Williams Eloise (Orcid ID: 0000-0002-0594-0056)

Title page

i) Title: Delays in presentation and diagnosis of pulmonary tuberculosis: a retrospective study of a tertiary health service in Western Melbourne, 2011-2014

ii) Author details:

1. Dr. Eloise Williams; MBBS, BMedSci, MPHTM
    a. *Current position*: Infectious Diseases Registrar; Alfred Health, Infectious Diseases, 55 Commercial Rd, Prahran VIC 3004
    b. *Affiliation at which work was carried out*: Western Health, Infectious Diseases, Gordon St, Footscray VIC 3011
    c. *Author's contribution:* Substantial contribution to design of the work, acquisition, analysis and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published and agreement to be accountable for all aspects of the work.
2. Prof. Allen Cheng; MBBS, FRACP, MPH, MBiostat, PhD
    a. *Current position:* Professor of Infectious Diseases Epidemiology and Director of the Infection Prevention and Healthcare Epidemiology Unit; Monash University Faculty of Medicine Nursing and Health Sciences, Department of Epidemiology and Preventive Medicine, 99 Commercial Rd, Prahran, VIC 3004
    b. *Affiliation at which work was carried out: as above*
    c. *Author's contribution:* Substantial contribution to analysis and interpretation of data for the work; drafting the work and revising it

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/imj.13551

critically for important intellectual content; final approval of the version to be published and agreement to be accountable for all aspects of the work.

3. Assoc. Prof. Garry P Lane; MBBS (Hons), FRACP, MMedSci, MQIHC
    a. *Current position:* Director of Infectious Diseases and Director of Clinical Services, Western Health, Infectious Diseases, Gordon St, Footscray VIC 3011
    b. *Affiliation at which work was carried out: as above*
    c. *Author's contribution:* Substantial contribution to the conception and design of the work and interpretation of data for the work, revising it critically for important intellectual content, final approval of the version to be published and agreement to be accountable for all aspects of the work.
4. Dr. Stephen David Guy; MBBS (Hons), FRACP
    a. *Current Position:* Infectious Diseases Physician, Western Health, Infectious Diseases, Gordon St, Footscray VIC 3011
    b. *Affiliation at which work was carried out: as above*
    c. *Author's contribution:* Substantial contribution to the design of the work, analysis and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published and agreement to be accountable for all aspects of the work.

iii) Corresponding author:

1. Eloise Williams
    a. Address: Alfred Health, Infectious Diseases, 55 Commercial Rd, Prahran VIC 3004
    b. Email address: eloise.williams@alfred.org.au
    c. Telephone number: (03) 9076 2000

iv) Acknowledgements:

- No financial grants or other funding was received for this work.
- We acknowledge the Victorian Tuberculosis Program for their assistance with case finding through the provision of tuberculosis notification data.

v) Word count:

- Abstract: 245 words
- Main text: 2782

vi) Abstract:

Background: Effective tuberculosis (TB) control relies on early diagnosis and prompt treatment commencement.

Aim: To investigate delays in presentation and diagnosis of pulmonary TB (PTB) in a low incidence setting in western Melbourne.

Methods: A single-centered retrospective observational cohort study of symptomatic patients ≥ 18 years newly diagnosed with PTB that were commenced on treatment between 1st December 2011 and 1st December 2014 at a tertiary teaching hospital in western Melbourne. Main outcome measures included median duration of patient, health system and total delays to diagnosis of PTB; and clinical factors associated with prolonged patient (>35 days) and health system (>21 days) delay.

Results: 133 patients were included. The median [range] duration of patient, health system and total delay to diagnosis were 28 [0-610], 18 [0-357] and 89 [1-730] days, respectively. Prolonged patient delay was associated with being from a country with an annual TB incidence of <50/100 000 (OR 5.98, 95% CI 1.19, 29.98) and diabetes mellitus (OR 3.02, 95% CI 1.04, 8.78) in multivariate analysis. Being Australian-born or resident in Australia ≥6 years (OR 0.03, 95% CI 0.12, 0.74; OR 0.30, 95% CI 0.00, 0.033, respectively) was associated with reduced patient delay.

Conclusions: In this low-incidence, high-resource setting, patient delays contribute most to total delay in PTB diagnosis. Strategies addressing this aspect of the TB diagnosis pathway, such as health literacy and promotion programs for new migrants and raised primary healthcare awareness could have the largest impact on reducing total PTB diagnosis delays.

vii) Key words:

Tuberculosis, Pulmonary; Pneumonia; Tuberculosis; Epidemiology; Communicable Disease Control

Williams Eloise (Orcid ID: 0000-0002-0594-0056)

19

"Delays in presentation and diagnosis of pulmonary tuberculosis: a retrospective study of a tertiary health service in Western Melbourne, 2011-2014"

i) Text:

Introduction:

Tuberculosis (TB) is a major global health problem; an estimated 10.4 million people developed TB in 2015 and 1.4 million people died from the disease[1]. Early diagnosis and prompt commencement of treatment are important for effective tuberculosis control. Delayed diagnosis may worsen the severity of disease and increase the risk of death[2].

Australia has maintained an annual incidence rate of active TB of 5.2 to 7.0 cases per 100, 000 since the mid-1980s[3]. Of the 1263 notified cases (nationally) in 2013, 58% had pulmonary tuberculosis (PTB)[3]. Over the past decade Australia has experienced a modest increase in TB incidence, from a rate of 5 per 100, 000 in 2003 to 6.2 per 100, 000 in 2011. This is likely due to an increasing migrant population from high incidence regions of the world; 88% of patients diagnosed with TB in Australia in 2013 were born overseas[3]. In comparison to the risk of active TB (over the past 10 years) in the Australian-born population of approximately 1 in 100,000[3], the risk for Australian immigrants reflects the TB incidence in the individual's country of origin[4]. The risk of active TB is highest for individuals in the first 6 years after migration, and approximates 100-150 per 100, 000 person-years for those from Asia, Africa and the Pacific during this period. Risk then falls to approximately 50 per 100, 000 person-years by 12 years[4].

A number of studies in various international settings have investigated time delays in diagnosis of PTB. Delays may occur before medical presentation ("patient" delays) or after medical presentation ("health system" delay). However, there is no consistent definition of 'delayed' (i.e. prolonged time until) diagnosis for PTB in the international literature. Previous studies have arbitrarily nominated a certain number of days from onset of symptoms to differentiate 'delayed' from 'acceptable' time periods; the number of days constituting 'delayed diagnosis' however has varied widely. Definitions of total delay has varied from 28 to 98 days[5,6,7,8,9,10]; patient delays have been defined variously from 30 to 60 days[7,8,10,];and health system delays from 7 to 56 days[7,8,10,11].

Since the last study of delayed diagnosis in Australia 15 years ago[9] there have been major socio-demographic changes in the Australian population, and new rapid tests for TB based on nucleic acid detection. We sought to explore factors associated with diagnostic delays in a large community hospital in Western Melbourne between 2011-2014.

Methods:

Study design and setting

A retrospective cohort study of patients diagnosed and treated for PTB at a single health service in Victoria was undertaken between 1st December 2011 and 1st December 2014. Western Health is a multi-campus tertiary health service in the western suburbs of Melbourne (Victoria) that provides health-care services to a population of approximately 800,000 people. Western Health treats approximately 25-30% of Victoria's approximately 350 cases of TB each year.

Case finding, inclusion and exclusion criteria

Patients were identified by two methods: a hospital database of discharge coding, and notification data from the Victorian Tuberculosis Program. In Victoria, notification of confirmed cases of TB is required under state legislation. The medical records of all additional cases identified by Western Health Australian Discharge Related Group (A-DRG) codes for pulmonary or miliary TB (ICD-10-AM codes A15, A16 and A19) were reviewed.

Patients were included if they were symptomatic with PTB, including disseminated TB with lung involvement or extra-pulmonary TB at a contiguous site combined with PTB, and commenced on treatment between 1st December 2011 and 1st December 2014. Patients under 18 years, those with extra-pulmonary TB without pulmonary involvement and asymptomatic patients were excluded.

Definitions of delays and prolonged delays

Initial health care contact was defined as the date the patient reported attending a health care provider, whether in primary care, or hospital-based secondary or tertiary health services. The date of 'diagnosis' was defined as the date of commencing anti-tuberculous therapy consistent with previous studies. Patient delay was defined as the time of onset of symptoms suggestive of PTB until initial health care contact; health system delay as the time from first initial health care contact until diagnosis; hospital delay as time from hospital admission to diagnosis. Total delay was the sum of patient delay and health system delay. We defined a *prolonged* patient delay and *prolonged* health system delay as a duration greater than the median of the sample population, rounded up to the nearest 1 week.

Countries of origin were defined as high risk if the annual incidence of tuberculosis was ≥50/100 000, and low risk if the annual incidence of tuberculosis was <50/100 000 according to the WHO Global TB report, 2014[15]. The nucleic acid test (NAT) used for rapid molecular diagnosis of TB in this population was the GeneXpert ® MTB/RIF, a fully automated DNA-PCR technique for detection of TB and rifampicin resistance mutations.

Statistical analysis

Univariate and multivariate regression analyses were performed to determine factors associated with prolonged delays. Univariate analyses were performed first, and factors with $p<0.2$ were considered for further analysis in the multivariate analysis. For final model selection, a modified backwards stepwise selection process was used, checking the effect of dropping variables on other odds ratios to obtain a parsimonious model. For all tests, two-sided p-values with alpha ≤0.05 level of significance were used.

Ethical considerations

This study was approved by the Western Health Low Risk Human Research Ethics Panel prior to commencement of the study (Project number LNR/15/WH/24)

Results:

Patient inclusion

Of 331 patients identified, a total of 133 patients met eligibility criteria and were included in the study (Figure 1). Notably, 37 patients were excluded due to asymptomatic PTB, which may be more common at this health service due to its role as the coordinating centre for visa screening of Chest X-ray (CXR) abnormalities in Victoria.

Patient demographics

Of these 133 patients, median age was 35 years and 67% were male (Table 1). Most spoke a language other than English at home (90%) and were born overseas (92%), most commonly from the Western Pacific Region, particularly from Vietnam (Figure 2). Eighty-five percent (85%) had migrated from a high risk country and 44% had resided in Australia <6 years. Only two (2%) were HIV positive.

Radiology

One hundred and thirty patients had a CXR available, with median time from CXR to diagnosis 13 days [IQR 4-36 days]. One hundred and six (80%) had CXR features suspicious of active PTB (Table 2). Eighty two (62%) patients had computed tomography (CT) of the chest performed, with a median time from CT until diagnosis 9 days [IQR 2-29]. All 82 patients who underwent CT chest had abnormalities found.

Microbiology

One hundred and ten patients had expectorated sputa sent for acid-fast bacilli (AFB) smear and mycobacterial culture; 39 (36%) patients had a positive AFB smear and 86 (78%) a positive sputum mycobacterial culture (Table 2). Median time from sputum assay to diagnosis was 4 days [IQR 2-29 days]. Fifty-seven (43%) patients underwent bronchoscopy; median time from bronchoscopy until diagnosis was 4 days [IQR 1-13]. Fifty-seven patients had NAT performed on sputum; 47 (83%) of these were positive. In those who had NAT performed on sputa, the yield of positive NAT in AFB smear positive sputa was 33/35 (94%), while the yield of positive NAT on smear negative sputa was 14/27 (52%). Forty-six patients (81%) patients who had a bronchoscopy had NAT performed on the bronchoscopy specimen. The yield of positive NAT on smear positive bronchoscopy specimens was 6/6 (100%), while the yield of positive NAT on smear negative bronchoscopy specimens was 23/40 (58%). Of the 26 patients with a prospectively collected NAT, median time from NAT to diagnosis was 1 day [IQR 0-1 days].

Delays

Patient delay was the predominant delay with a median of 28 days from symptom onset until first health service contact (Table 3). Median health system delay was 18 days. We therefore defined a prolonged patient delay as more than 35 days and a prolonged health system delay as more than 21 days. According to this definition, 55/133 (41.3%) of patients in this study had a prolonged patient delay and 59/133 (44.4%) had a prolonged health system delay.

Prolonged patient delay

In univariate analysis, prolonged patient delay was associated with weight loss (OR 2.16, 95% CI 1.06, 4.43) and inversely associated with presence of fatigue (OR 0.41, 95% CI 0.16, 0.99) (Table 4). In multivariate analysis, migration from a low risk annual TB incidence country (OR 5.98, 95% CI 1.19, 29.98) was the strongest predictor of patient delay (figure 3). Weight loss (OR 2.23, 95% CI 1.00, 4.96) and diabetes mellitus (OR 3.02, 95% CI 1.04, 8.78) were also associated with prolonged patient delay. Conversely, migration to Australia ≥ 6 years prior or being Australian born were associated with reduced patient delay (OR 0.30, 95% CI 0.12, 0.74; OR 0.03, 95% CI 0.00, 0.33 respectively).

Prolonged health system delay

In univariate analysis, patient age 65 years or older (OR 3.07, 95% CI 1.21, 7.79) (Figure 4) and patient review in outpatient clinic (OR 7.67, 95% CI 3.51, 16.77) were associated with prolonged health system delay (Table 5). Factors associated with reduced risk of prolonged health system delay were presence of cough (OR 0.09, 95% CI 0.01, 0.72), review in the emergency department (OR 0.33, 95% CI 0.16, 0.69) or admission to hospital (OR 0.17, p 95% CI 0.06, 0.46). Additionally, for patients who were able to expectorate sputum, AFB smear positivity (OR 0.23, 95% CI 0.09, 0.56) and NAT positivity (OR 0.14, 95% CI 0.03, 0.62) were associated with reduced risk of prolonged health system delay. Patients who had positive sputum NAT had a median health system delay of 9 days, compared with a median health system delay of 41 days in those who had a negative sputum NAT and 21 days in those who did not have a sputum sent for NAT. Having cavitating lesions on CXR (OR 0.25, 95% CI 0.09, 0.67) was also associated with reduced health system delay.

In multivariate analysis, patient age 65 or older was associated with prolonged health system delay (OR 4.29, 95% CI 1.55, 11.89), while presence of cough (OR 0.09, 95% CI

0.01, 0.79) and being admitted to hospital were associated with reduced health system delays (OR 0.28, 95% CI 0.09, 0.92).

Discussion:

This single-centre retrospective review of delays in diagnosis of PTB in Western Melbourne illustrated that delays between symptom onset and treatment commencement are predominantly due to patient delay in presentation for care. The median duration of delays found in this study align with those found in an international systematic review of the topic in 2009, which included 52 studies and found an average patient delay of 28.7 days and average health system delay of 25 days[12]. Findings are also comparable to the latest studies conducted in Australia on this topic[9,,13].

A study published in 2001[9] included 782 symptomatic, culture positive cases of PTB based on Queensland Tuberculosis Control Centre TB case notification form data between 1985-1998. Median patient delay in this study was 29 days and median health system delay 22 days. Despite advances in rapid diagnosis, delays are only marginally shorter than those described 15 years ago. A recently published study by Dale et al[13] involved 5106 Victorian patients identified through notification form data between 2002 and 2015 with PTB and extra-pulmonary TB and compared the management of patients receiving private versus public healthcare. The median patient delay was 18 days and median health care delay was 22 days in those receiving public healthcare in this cohort. The duration of health care delay found by Dale et al correlates well with our study. The discrepancy in patient delay between our study and that by Dale et al may be a factor of information bias, with duration of symptoms prior to health care contact perhaps being less accurately recorded on a notification form compared to a more detailed file review; or it may be due to socioeconomic factors specific to the community served by this single centre health service.

Of significant interest in our study population was the wide range of patient and health system delays that occurred. Whilst this will not impact on the median delays for each locus of delay, when total delay is considered, a substantial increase in delay occurs. A quarter of patients had patient delays between 90 and 610 days and health system delays between 53 and 357 days. Whilst in our subsequent analysis, various delays have been analysed regarding their potential to reduce time to diagnosis, perhaps the biggest impact overall could be achieved by expediting diagnosis of the quartile of individuals who experience very long delays.

In this study, migration from a country with annual TB incidence of <50/100,000 population was the strongest predictor of patient delay, although only 7% of patients fell into this group. Whilst several putative explanations for this exist, it is possible that people from these 'low-risk' countries, especially those resident in Australia <6 years may be less aware of TB as a disease state, whilst still in the higher risk time period to develop active disease post migration. Recent migrants from high-risk countries also had a longer delay than Australian-born patients, whereas Australian-born patients and those residing in Australia >6 years had reduced risk of delay. This may be due to greater health literacy and English language skills in longer-term residents and Australian-born individuals facilitating access to health-care. We speculate that poor access to health care, poor health literacy, fear that TB diagnosis could impact on visa and residency status within Australia, fear of associated costs of health-care (even though TB services are provided free to all patients within Victoria), or stigma and misunderstanding about TB diagnosis and treatment may disproportionately affect recent migrants, and that structural barriers to TB care may exist.

Prolonged health system delay was more common in older patients, a finding common to a number of similar studies, including the previous Australian study[9]. Predictably, there was a reduced risk of prolonged health care delay in those with classical symptoms of cough, cavitating features on CXR and sputum AFB smear positivity. A positive sputum NAT was also associated with a shorter health system delay in this study. While delays were much shorter in patients admitted to hospital for investigation, this is likely to be confounded by the severity of illness and reverse causation (where patients are admitted because of a higher likelihood of TB and/or positive tests). Recommendations regarding where patients should be assessed for TB workup is therefore not possible from this data set.

NAT and other molecular diagnostics appear to offer some utility in reducing diagnostic delays and may be the first of several new diagnostic tools available over the coming years. Vital to any strategy to reduce health system delay will be clinician education and awareness, consideration of PTB as a disease process and appropriately resourced facilities for diagnosis and management of PTB.

The limitations of this study include its retrospective nature, making it vulnerable to recall bias, with data concerning primary outcomes based on hospital records of symptom onset and nature recorded by medical officers rather than directly from patients. It was also limited to a single centre, which raises the possibility that findings are specific for this site however it is reassuring that a similar duration of health system delay was found in the recently conducted study by Dale et al.

Conclusion:

This study demonstrates that patient delay remains the biggest delay in diagnosis of PTB, consistent with published literature. For greatest overall impact on reducing delays until TB diagnosis, strategies should continue to target migrants, especially those from high-risk countries, at several time points within their first years of residence within Australia. These may include health literacy programs that assist new migrants with navigating the Australian health-care system, and information regarding TB disease, treatment and costs. These messages need to be framed to reach these populations most at risk, in a culturally and linguistically contextualised manner. Engagement of community leaders with this issue to help disseminate these messages would be highly valuable. A letter to new migrants in the appropriate language explaining the importance of TB, the symptoms of active disease and that diagnosis and treatment will not incur costs or affect visa status could be another useful tool to address prolonged patient delays. The Australian Government Department of Immigration and Border Protection has developed an excellent information webpage[14] in a number of languages for international students that could be more widely disseminated to all new migrants to Australia. Given that only 19.5% of patients in this cohort identified as students, disseminating this information more widely could have a powerful effect. Additionally, health-care providers to this group of patients require knowledge on TB disease, presentation and diagnostics, since likelihood differs significantly from Australian born individuals.

ii) References

1. World Health Organization. Global Tuberculosis Report 2016. Geneva: World Health Organization. 2016 [cited 2016 Dec 12]. Available from: http://www.who.int/tb/publications/global_report/en/

2. TB CARE I. International Standards for Tuberculosis Care (3rd edition). The Hague: TB CARE I. 2014 [cited 2015 August 15] Available from: http://www.who.int/tb/publications/ISTC_3rdEd.pdf

3. Toms C, Stapledon R, Waring J, Douglas P, the National Tuberculosis Advisory Committee for the Communicable Diseases Network Australia, the Australian Mycobacterium Reference Laboratory Network. Tuberculosis Notifications in Australia, 2012 and 2013. Commun Dis Intell. 2015; 39(2): E217-E235

4. McBryde ES, Denholm JT. Risk of active tuberculosis in immigrants: effects of age, region of origin and time since arrival in a low-exposure setting. Med J Aust. 2012; 197(8): 458-461

5. Phoa LL, Teleman MD, Wang YT, Chee CBE. Characteristics of patients with delayed diagnosis of infectious pulmonary tuberculosis. Respirology. 2005, 10: 196-200

6. Jurcev-Savicevic A, Mulic R, Kozul K, Bozica B, Valic J, Bacun-Ivcek L et al. Health system delay in pulmonary tuberculosis treatment in a country with an intermediate burden of tuberculosis: a cross-sectional study. BMC Public Health. 2013;13:250-263

7. Lin CY, Lin WR, Chen TC, Lu PL, Huang PM, Tsai ZR et al. Why is in-hospital diagnosis of pulmonary tuberculosis delayed in Southern Taiwan? J Formos Med Assoc. 2010, 109(4): 269-277

8. Ohmori M, Ozasa K, Mori T, Wada M, Yoshiyama T, Aoki M et al. Trends of delays in tuberculosis case finding in Japan and associated factors. Int J Tuberc Lung Dis. 2005; 9(9): 999-1005

9. Ward J, Siskind V, Kostantinos A. Patient and health care system delays in Queensland tuberculosis patients, 1985-1998. Int J Tuberc Lung Dis. 2001; 5(11): 1021-1027

10. Sendagire I, Van der Loeff MS, Mubiru M, Konde-Lule J, Cobelens F. Long delays and missed opportunities in diagnosing smear-positive pulmonary tuberculosis in Kampala, Uganda: a cross-sectional study. PLoS ONE 5(12): e14459

11. Craig SE, Bettinson SH, Sabin CA, Gillespie SH, Lipman MCI. Think TB! Is the diagnosis of pulmonary tuberculosis delayed by the use of antibiotics. Int J Tuberc and Lung Dis. 2009; 13(2): 209-213

12. Sreeramareddy CT, Panduru KV, Menten J, Van den Ende J. Time delays in diagnosis of pulmonary tuberculosis: a systematic review of the literature. BMC Infectious Diseases. 2009; 9:91-101

13. Dale KD, Tay EL, Trauer JM, Trevan PG, Denholm JT. Comparing tuberculosis management under public and private healthcare providers: Victoria, Australia, 2002-2015. BMC Infectious Diseases, 2017; 17: 324-336

14. Australian Government Department of Immigration and Border Protection. [homepage on the internet]. Tuberculosis warning for international students. [cited 1st June 2017]. Available at https://www.border.gov.au/Trav/Stud/More/tuberculosis

iii) Figure legends

Figure 1. Patient inclusion flow diagram

Figure 2. Patient country of birth, categorized by WHO Region*:*

WHO Regions: SEARO: South-East Asia Regional Office; WPRO: Western Pacific Regional Office; EMRO: Eastern Mediterranean Regional Office; AFRO: Africa Regional Office; EURO: Europe Regional Office; PAHO: Americas Regional Office

Figure 3. Kaplan-Meier curve of patient delay in patients by TB risk in country of birth

Figure 4. Kaplan-Meier curve of health system related delays by age

v) Tables

Table 1. Patient Demographic Characteristics

Characteristic	Patients (n = 133)
Age	
Median [IQR]	35 [26-57]
Demographics	*n (%)*
Male	89 (67%)
Native Language English	13 (10%)
Employed	47 (35%)
Time since migration	
Australian born	11 (8%)
Less than 6 years	59 (44%)
6 or more years	63 (47%)
Migration risk	
Australian born	11 (8%)
Low risk country	9 (7%)
High risk country	113 (85%)
Symptoms	
Cough	124 (93%)
Productive cough	86 (65%)
Haemoptysis	25 (19%)
Dyspnoea	38 (29%)
Chest pain	38 (29%)
Weight loss	75 (56%)
Sweats	50 (38%)
Fevers	75 (56%)
Fatigue	31 (23%)
Comorbidities	
Current smoking	48 (36%)
Excessive alcohol intake	18 (14%)
Diabetes mellitus	31 (23%)
Chronic liver disease	12 (9%)
Asthma/COPD	18 (14%)
Malignancy	7 (5%)
HIV positive	2 (2%)
Injecting drug use	5 (4%)

IQR: Inter-quartile range; COPD: chronic obstructive pulmonary disease

Table 2. Diagnostic and Outcome Data

Characteristic	**Patients (n = 133)**
Microbiology	
Sputum	110/133
AFB smear positive	39/110 (36%)
Mycobacterial culture positive	86/110 (78%)
NAT positive	47/57 (83%)
Bronchoscopy specimen	57/133 (43%)
AFB smear positive	9/57 (16%)
Mycobacterial culture positive	42/53 (79%)
NAT positive	29/43 (67%)
Overall microbiology	122/133 (92%)
Positive	11/133 (8%)
Negative	
Radiology*	
CXR available	130/133 (98%)
CXR suggests active PTB	106/130 (82%)
CXR - cavitation	29/130 (22%)
CT chest performed	82/133 (62%)
CT chest abnormal	82/82 (100%)
Diagnosis	
Pulmonary TB	97 (73%)
Disseminated TB	16 (12%)
Pulmonary TB with contiguous extra-pulmonary involvement	20 (15%)
Outcome	
Completed treatment	118 (89%)
Continues treatment	1 (1%)
Treated at another site	7 (5%)
Lost to follow-up	3 (2%)
Died	4 (3%)

AFB = Acid fast bacilli; NAT = Nucleic acid test;
CXR = Chest X-Ray; TB = tuberculosis;
PTB = pulmonary tuberculosis
** Radiological features not mutually exclusive*

Table 3. TB diagnosis delays

Primary outcome (days)	Median [IQR]	Range
Patient delay	28 [13-90]	0-610
Health system delay	18 [7-53]	0-357
Hospital delay	4 [2- 9]	0-159
Total delay	89 [33-151]	2-730

IQR: Inter-quartile range

Table 4. Risk factors for prolonged patient delay

Variable		***Univariate analysis***		***Multivariate analysis***	
	n (%)	***OR (95% CI)***	***p***	***OR (95% CI)***	***p***
Age					
≥ 65 years *<65 years*	12/24 (50%) 43/109 (39%)	1.53 (0.63, 73)	0.34		
Sex					
Female *Male*	17/44 (39%) 38/89 (43%)	0.85 (0.40, 1.77)	0.66		
English spoken at home					
Yes *No*	3/13 (23%) 52/120 (43%)	0.39 (0.10, 1.50)	0.16	NI	
Employment					
Working *Not working*	18/47 (38%) 37/86 (43%)	0.82 (0.40, 1.70)	0.60		
Time since migration					
<6 years *≥6 years* *No migration*	29/59 (49%) 24/63 (38%) 2/11 (18%)	1.00 0.63 (0.29, 1.39) 0.22 (0.02, 1.27)		1.00 0.30 (0.12, 0.74) 0.03 (0.00, 0.33)	 **0.01** **<0.01**
TB risk in country of migration					
High risk Low risk No migration	47/113 (42%) 6/9 (67%) 2/11 (18%)	1.00 2.81 (0.56, 18.1) 0.31 (0.03, 1.62)		1.00 5.98 [1.19, 29.98) -	**0.03**
Cough					
Yes *No*	52/124 (42%) 3/9 (33%)	1.44 (0.35, 6.04)	0.61		
Haemoptysis					
Yes *No*	12/25 (48%) 43/108 (40%)	1.40 (0.58, 3.34)	0.45		
Dyspnoea					
Yes *No*	12/38 (32%) 43/95 (45%)	0.56 (0.25, 1.24)	0.15	NI	
Chest pain					
Yes *No*	11/38 (29%) 44/95 (46%)	0.47 (0.21, 1.06)	0.07	NI	
Weight loss					
Yes *No*	37/75 (49%) 18/58 (31%)	2.16 (1.06, 4.43)	**0.03**	2.23 (1.00, 4.96)	**0.05**
Sweats					
Yes *No*	18/50 (36%) 37/83 (45%)	0.70 (0.34, 1.44)	0.33		
Fevers					
Yes *No*	29/75 (39%) 26/58 (45%)	0.78 (0.39, 1.56)	0.47		
Fatigue					

Yes *No*	8/31 (26%) 47/102 (46%)	0.41 (0.16, 0.99)	**0.05**	NI	
Diabetes Mellitus					
Yes *No*	12/21 (57%) 43/112 (38%)	2.14 (0.83, 5.50)	0.11	3.02 (1.04, 8.78)	**0.04**
Baseline eGFR <60 ml/min					
Yes *No*	3/5 (60%) 52/128 (41%)	2.19 (0.35, 13.59)	0.39		
Chronic liver disease					
Yes *No*	6/12 (50%) 49/121 (40%)	1.47 (0.45, 4.82)	0.52		
Asthma/COPD					
Yes *No*	4/13 (31%) 51/120 (43%)	0.60 (0.18, 2.06)	0.42		
Current smoking					
Yes ***No***	24/48 (50%) 31/85 (64%)	1.74 (0.85, 3.57)	0.13	2.27 (0.99, 5.18) 1.00	**0.05**
Hazardous alcohol intake					
Yes *No*	11/18 (61%) 44/115 (38%)	2.53 (0.92, 7.03)	0.07	NI	

NI: not included in final model; OR: Odds ratio; 95% CI: 95% Confidence interval; TB: tuberculosis; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate

Table 5. Risk factors for prolonged health system delay

Variable	***Univariate analysis***			***Multivariate analysis***	
	n (%)	***OR (95% CI)***	***p***	***OR (95% CI)***	***p***
Age					
≥ 65 years *<65 years*	16/24 (67%) 43/109 (39%)	3.07 (1.21, 7.79)	**0.02**	4.29 (1.55, 11.89)	**0.01**
Sex					
Female *Male*	20/44 (46%) 39/89 (43%)	1.07 (0.52, 2.21)	0.86		
English spoken at home					
Yes *No*	5/13 (39%) 54/120 (45)	0.76 (0.24, 2.47)	0.65		
Australian born					
Yes *No*	3/11 (8%) 56/122 (46%)	0.44 (0.11, 1.75)	0.23		
Employment					
Working *Not working*	16/47 (34%) 43/86 (50%)	0.52 (0.25, 1.08)	0.08	NI	
Cough					
Yes *No*	51/124 (41%) 8/9 (89%)	0.09 (0.01, 0.72)	**0.01**	0.09 (0.01, 0.79)	**0.03**
Haemoptysis					
Yes *No*	7/25 (28%) 52/108 (48%)	0.42 (0.16, 1.08)	0.07	NI	
Dyspnoea					
Yes *No*	17/38 (45%) 42/95 (44%)	1.02 (0.48, 2.18)	0.96		
Chest pain					
Yes *No*	12/38 (32%) 47/95 (50%)	0.47 (.021, 1.04)	0.06	NI	
Weight loss					
Yes *No*	33/75 (44%) 26/58 (45%)	0.97 (0.49, 1.93)	0.92		
Sweats					
Yes *No*	22/50 (44%) 37/83 (62%)	0.98 (0.48, 1.98)	0.95		
Fevers					
Yes *No*	30/75 (40%) 29/58 (50%)	0.67 (0.33, 1.33)	0.25		
Fatigue					
Yes *No*	9/31 (29%) 50/102 (47%)	0.43 (0.18, 1.01)	**0.05**	NI	
Local Medical Officer review					
Yes *No*	44/94 (47%) 15/39 (25%)	1.41 (0.66, 30.2)	0.38		

Emergency Department review					
Yes *No*	27/80 (34%) 32/53 (60%)	0.33 (0.16, 0.69)	**<0.01**	0.43 (0.17, 1.07)	0.07
Outpatients review					
Yes *No*	39/54 (72%) 20/79 (25%)	7.67 (3.51, 16.77)	**<0.001**	NI	
Hospital Admission					
Yes *No*	39/107 (36%) 20/26 (77%)	0.17 (0.06, 0.46)	**<0.001**	0.28 (0.09, 0.92)	**0.04**
Current smoking					
Yes *No*	16/48 (33%) 43/85 (51%)	0.49 (0.23, 1.01)	**0.05**	NI	
Excessive alcohol intake					
Yes *No*	6/18 (33%) 53/115 (46%)	0.59 (0.21, 1.67)	0.31		
CXR shows cavity					
Yes *No*	6/29 (21%) 53/104 (51%)	0.25 (0.09, 0.67)	**<0.01**	NI	
Sputum AFB smear positive (n=110)					
Yes *No*	8/39 (21%) 38/71 (54%)	0.23 (0.09, 0.56)	**<0.01**	NI	
Sputum mycobacterial culture positive (n=110)					
Yes ***No***	33/86 (38%) 13/24 (54%)	0.53 (0.21, 1.31)	0.17	NI	
Sputum NAT positive (n=58)					
Yes *No*	13/47 (28%) 8/11 (73%)	0.14 (0.03, 0.62)	**0.01**	NI	

NI: not included in final model; OR: Odds ratio; 95% CI: 95% Confidence interval; CXR: Chest X-Ray; AFB: Acid fast bacilli; NAT: nucleic acid test