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Estimating long-term tuberculosis reactivation rates in Australian migrants

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Summary:

We estimated TB reactivation rates in Australian migrants by combining time and country-specific infection estimates with census and notification data. Post-migration reactivation rates declined over time from migration, and also appeared to increase during youth (aged 15-24 years) and old-age.

Abstract

Background: The risk of progression to tuberculosis (TB) disease is greatest soon after infection, yet disease may occur many years or decades later. However, rates of TB reactivation long after infection remain poorly quantified. Australia is a low-TB incidence setting and most cases occur among migrants. We explored how TB rates in Australian migrants varied with time from migration, age and gender.

Methods: We combined TB notifications in census years 2006, 2011 and 2016 with time and country-specific estimates of latent TB prevalence in migrant cohorts to quantify post-migration reactivation rates.

Results: During the census years 3,246 TB cases occurred among an estimated 2,084,000 migrants with latent-TB. There were consistent trends in post-migration reactivation rates, which appeared to be dependent on both time from migration and age. Rates were lower in cohorts with increasing time until at least twenty years from migration, and on this background there also appeared to be increasing rates during youth (15-24 years of age), and in those aged 70 years and above. Within five years of migration, annual reactivation rates were approximately 400 per 100,000 (uncertainty interval [UI]: 320-480), dropping to 170 (UI: 130-220) and 110 (UI: 70-160) from five-to-ten and ten-to-twenty, then sustaining at 60-70 per 100,000 up to sixty years from migration. Rates varied depending on age at migration.

Conclusions: Post-migration reactivation rates appeared to show dependency on both time from migration and age. This approach to quantifying reactivation risk will enable evaluation of the potential impact of TB control and elimination strategies.

Introduction

Mycobacterium tuberculosis (*Mtb*) can persist in a latent state (latent TB infection, LTBI) and reactivate to cause tuberculosis disease (TB) many years or decades following infection [1]. However, there remains uncertainty regarding the magnitude of TB reactivation risk many years after infection. While there are evident challenges in long term quantification of risk, including the length of follow-up required, and the difficulty in definitively attributing infection to a particular exposure, this uncertainty has implications for understanding TB epidemiology, and in predicting the effectiveness of strategies for prevention of reactivation.

Australia is a low-TB incidence setting and for several decades has had high levels of migration from high-incidence countries. Overseas visa applicants over the age of ten have long been required to undertake a chest X-ray (CXR) to rule out active pulmonary disease, and those with evidence of old, inactive TB or a history of active TB attend further follow-up on-shore [2]. However, no systematic LTBI screening and treatment of migrants occurs that is likely to have a significant impact on TB control [3]. Given the low rates of *Mtb* transmission in Australia [4], the large majority of TB cases occur among migrants from high-burden settings and are likely to represent reactivation of LTBI acquired premigration [5]. While the timing of infection acquisition in migrants is often uncertain, the time of migration provides a point beyond which infection is much less likely to have occurred. Therefore, observing reactivation rates by time since migration in migrant cohorts provides an opportunity to study how TB rates change with time from infection.

Studies that have reported TB rates among migrants over time since migration to low-incidence settings have often found the greatest risk of disease in the first years after migration [6-9]. While some studies have shown decreasing TB rates beyond this period [6, 8], in other cohorts rates did not decrease uniformly over time [7, 10, 11]. Such variation in findings may relate to the heterogeneity of the migrant populations studied with regards to historical TB burden and time in their countries of birth, age at migration and age, each of which may influence infection risk. No

studies have yet considered TB rates over time in migrant cohorts whilst accounting for all of these predictors of infection risk.

We previously estimated the prevalence of LTBI in Australian migrants using country-specific data on annual risk of TB infection (ARTI) and applying them to national census data by country of birth, age and year of migration [12]. Here we combine these estimates with data on Australian TB notifications in migrants to better understand how TB reactivation rates vary with time since migration, as well as with gender and age.

Methods

Census data

Australian population data from the 2006, 2011 and 2016 censuses were exported from the Australian Bureau of Statistics (ABS) Table Builder [13] by country of birth, sex, age and year of migration. Residents without a designated country of birth or year of migration were excluded from analysis.

Notification data

Australian TB case data were obtained for each census year from Australian National Notifiable Diseases Surveillance System data (accessed 23/02/2018) by year and state of notification, country of birth, age, sex, site of disease and year of migration. In Australia a confirmed case of TB requires culture or polymerase chain reaction confirmation of *Mtb*, or diagnosis by a clinician experienced in TB management, including clinical follow-up to ensure a consistent clinical course [14].

Annual risks of infection and reactivation rates

The methods used to estimate Australian LTBI prevalence in the study years have been previously described [12, 15]. Briefly, for each of 168 countries and for each year from 1934 to 2014, simulated ARTI trajectories were estimated using data from tuberculin skin test (TST) surveys and/or WHO

Global TB Programme prevalence estimates (1990–2014), which were adjusted based on a revised Styblo ratio [15]. The prevalence of LTBI was estimated for each population cohort by country of birth, age and year of migration. In contrast to previous work, in this study we assumed that infection was acquired premigration and so assumed that the ARTI in Australia was zero. Furthermore, gender was a variable of interest in this analysis, although the prevalence of LTBI in arrival cohorts was assumed to be equal for each gender. Data on all Australian TB notifications from 1st January to 31st December in 2006, 2011 and 2016 were merged with the relevant census and LTBI prevalence data. Representative census groups were added for any unmatched notifications.

TB case numbers, the number estimated to have LTBI and total population numbers were aggregated over each cohort considered. TB notification rates were calculated as the number of TB notifications divided by the total population, with 95% confidence intervals calculated using the Poisson exact test. Post-migration reactivation rates were calculated as the annual number of TB cases in each population group divided by the median estimated prevalence of LTBI. Lower and upper uncertainty intervals (UI) are given by the upper and lower 95% confidence intervals of the Poisson exact test using the number of TB cases and the 75th and 25th percentiles of the LTBI prevalence estimates, respectively.

We use the term “reactivation” throughout to refer to all TB cases that occurred post-migration, although we acknowledge that an unknown number of TB cases may have been due to primary progression following recent infection acquired premigration, in Australia or during overseas travel. We use the term “migrant” to refer to anyone born outside Australia.

Australia’s Torres Strait Islands are close to Papua New Guinea (PNG) and The Torres Strait Treaty allows free movement of people between the countries for traditional activities [16]. Some PNG residents seek medical care in Australia and those with TB were included in Australia’s notification data during the study years [16]. Because these individuals were not Australian residents we

excluded all TB cases notified in Queensland and born in PNG from our analysis, recognising that this also would have excluded TB cases in PNG-born Queensland residents.

Sensitivity analyses

In LTBI prevalence calculations we assumed that ARTI was zero after migration. We assessed the impact of this assumption by recalculating reactivation rates assuming the risk of infection continued post-migration using Australian ARTI estimates [12].

We used 1934 ARTI estimates for all years prior to 1934. To ensure this assumption did not have any appreciable effect on our conclusions, we illustrate reactivation rates only in those migrants born in or after 1934.

We also assessed the likely impact of missing census data. To account for non-responding dwellings the ABS post-enumeration survey provides undercount adjustment factors with associated standard errors for census groups by age-group and sex and for selected countries of birth by sex (without year of migration information) [17-19]. We applied these factors to migrant cohort size estimates to assess the impact that excluding census non-respondents may have had on reactivation rates. The ABS applies perturbation to TableBuilder data to manage disclosure risk; we examined its effect by re-extracting data by fewer and grouped variables, applying grouped ARTI risks, and recalculating reactivation rates.

Year of migration was missing for some census and TB case data and we explored the possible impact of this on results using the predictive mean matching method to impute these values using the MICE package [20] and R, version 3.4.4 (Boston, MA).

Ethics statement

Data for this project was collected under relevant Australian jurisdictional public health legislation. Relevant database managers authorised the use of non-identifiable census and notification data.

According to the rules of our institutions, additional approval from an Institutional Ethics Committee was not required.

Results

The characteristics of the study cohort are presented in Table 1 and are disaggregated by census year in Table S1, together with details of missing data. Australian residents born in India, China, the Philippines and Vietnam made up the greatest number estimated to have LTBI in the census years (Table 1).

TB notification rates

The TB notification rates of migrants arriving in Australia in 2006, 2011 and 2016 were 114/100,000/year, 91/100,000/year and 82/100,000/year, respectively. Rates decreased with increasing time from migration, were higher in males than females and showed some age dependency (Figure 1a /b/c).

TB notification rates within the first five years after migration were broadly equivalent to, or lower than, the World Health Organization (WHO) birth country TB incidence estimates in each census year, and rates were largely lower again with increasing time from migration, but remained higher than the Australian TB notification rates, even in cohorts that had migrated more than twenty years earlier (Figure S1).

Reactivation rates

Of all Australian migrants estimated to have LTBI, the median TB reactivation rates were lower in cohorts with increasing time from migration to at least 20 years post-migration, after which it was uncertain whether further declines occurred (Figure 1d), with rates apparently stable around 60-70/100,000/year. In the first five years after migration, the average annual reactivation rate was 400/100,000 (UI 320-480). From five-to-ten, ten-to-twenty, twenty-to-forty and forty-to-sixty years

from migration rates were 170 (UI: 130-220), 110 (UI: 70-160), 70 (UI: 40-140) and 60 (UI: 20-190), respectively. However, reactivation rates also showed dependency on both age and gender (Figure 1e and Figure S2), such that rates varied depending on age at arrival, gender and time since migration (Figure 1e/f, Table 2 and Table S2).

There was little difference in these patterns over the three census years, although the rates in 2016 appeared slightly lower than the previous years (Figure S2).

Figure 2 presents post-migration reactivation rates by age at migration and age. The highest reactivation rates soon after migration were seen in young children, youth (15 to 24 years of age) and the elderly. Regardless of the age at migration, rates decreased in cohorts with increasing time from migration, although greater uncertainty was seen with increasing time from migration and in cohorts that had migrated under five or over 69 years of age. On the background of otherwise declining reactivation rates with time from migration, there also appeared to be increases in youth and those aged 70 years and over (Figure 2). Results further disaggregated by gender are shown in Figure S3, showing higher reactivation rates in males in some cohorts, particularly in the elderly. Similar trends were observed when considering pulmonary and extrapulmonary TB separately (Figure S4 and Figure 3).

When considering age-matched cohorts with LTBI from different countries of birth, the greatest variation in reactivation rates was seen in the first years after migration, while rates progressively converged with time from migration (Figure S5).

Sensitivity analysis

All sensitivity analyses resulted in negligible effects on reactivation rates and main findings. Applying Australian ARTI estimates following migration marginally lowered rates among cohorts who migrated >40 years ago (Figure S6); accounting for census non-respondents by applying the ABS post-enumeration survey undercounts marginally changed absolute reactivation rate estimates (typically by no more than 4.3%) (Figure S7); imputation of missing years of migration had a

negligible effect (unpublished data); ABS data re-extraction using grouped variables marginally reduced rates, particularly in the elderly (Figure S8) and excluding migrants born before 1933 also had a negligible effect on overall patterns and main findings (Figure S9).

Discussion

In our simulated cohort of Australian migrants with LTBI, TB reactivation rates appeared to be dependent on both time from migration and age, with lower rates seen with increasing time from migration and possible increases in rates in those aged 70 years and during youth. Although these trends are consistent with existing observations [9, 21-25], to our knowledge, this is the first time all these phenomena have been demonstrated in a single study, and the first study to use estimated LTBI prevalence among migrant populations to provide insights into the natural history of TB. While Australian migrant populations are highly heterogeneous and the reasons for TB reactivation may be multi-factorial and complex, *Mtb* infection is the only absolute prerequisite for reactivation, and our study demonstrates that taking into account infection risk can clarify average reactivation risk in such heterogeneous populations. Furthermore, the quantification of post-migration reactivation rates will be useful in the planning of targeted TB control strategies.

Our results confirmed that the passing of time from migration had an impact on reactivation rates. Lower rates were observed in cohorts that had migrated longer ago, whether comparing across birth cohorts or cohorts who had all migrated at a similar age, and long term rates were consistent with reactivation rate estimates made by Shea *et al.* 2014 in US migrant cohorts [23]. In our low-incidence setting the lower rates seen with increasing time from migration is likely to indicate that disease risk declines with increasing time from infection; and this observation has also recently been made regarding US migrants [22]. Further, with TB reactivation rates highest soon after infection, differences in the proportion of cohorts that had been recently or remotely infected premigration is likely to explain the varying reactivation rates seen in migrant cohorts from different countries in the early years following migration. This effect may also explain the slightly lower rates seen in the latest

census year, because TB incidence in many of the countries where recent migrants were born has declined slightly over time. Additional explanations for these observations could include different off-shore premigration TB detection practices, or changes in the migrant mix from countries that may have influenced their premigration infection or progression risk. Post-migration reactivation rates may also partially reflect the different living conditions that many new migrants experience [21].

In addition to time, there were also indications in our results that the risk of progression may differ along life course, with higher reactivation rates in elderly cohorts and youth when compared to younger cohorts that had migrated at a similar age. These observations have been made before [9, 25-31], and the pattern of pulmonary TB reactivation rates we observed by age post-migration resembles that of a study in Ontario, Canada that compared TST-survey data from 1958 to 1960 to pulmonary TB cases across the same region in 1962 (Figure S10) [21]. Further evidence that reactivation rates may increase into old age can also be observed in other studies [32, 33], including birth cohort studies [30, 31] and a recent study in Canadian migrants [9], and plausible reasons may include weakened immune status and increasing prevalence of comorbidities associated with old age [34-36]. Previous studies have also observed a period of increased reactivation risk during youth [25-29], but whether these increases are due to reactivation of quiescent infections, or an increased risk of reinfection is debateable. Our study provides additional evidence for this debate from a low-incidence setting, but we also cannot exclude that an increased risk of reinfection into youth led to the few cases that caused these observations in our setting. This is because of the following important assumption/limitation of our study.

Our study design assumes that all TB cases in the study cohort arose from reactivation of latent infection acquired premigration. However, some will have resulted from infection acquired post-migration during either local transmission [4] or travel overseas, or from relapsed TB cases [37]. Previously published studies in Victoria support low rates of local transmission (4.2% of culture-

confirmed TB cases from 2003-2010 “likely” to be due to local transmission) [4] and relapse [37], but genotypic and epidemiological information were not available for all Australian TB cases. Because we could not exclude cases due to local transmission, overseas travel or relapse, some presented reactivation rates will overestimate the contribution of infection that was acquired premigration. National genotyping studies and studies that refine estimates of travel-associated risk by age will be valuable in the future, and will help to clarify the effect of age on reactivation rates.

A discussion of the limitations of the original modelled LTBI prevalences can be found in our previous publications [12, 15]. Particularly pertinent to the current results is that we uniformly applied ARTI estimates by country of birth, year and gender, but acknowledge that infection risk is likely to vary within countries between populations and by age and gender [21, 38]. For example, while we observed higher reactivation rates in males, which is in line with wider observations of TB incidence [39], the relative importance of differential infection or progression risk or ability to clear infection [24], in our study cohort is unknown.

Our study also assumed that untreated LTBI persists lifelong. However, there is evidence to suggest that LTBI may naturally resolve over time (e.g. TST reversion) [21, 40, 41], and, if so, our estimates may increasingly underestimate rates among contemporary TST reactors with time. Additionally, data on comorbidities such as HIV or diabetes were not considered, limiting generalisability of our results to settings with a different frequency of risk factors.

Despite the limitations, our method also has a number of important strengths. In contrast to observational studies among TB contacts, which usually have small samples, seldom have more than two years of follow up, and are complicated by the provision of preventive treatment, an estimated two million migrants were included in our analysis, time since migration spanned decades, and migrants were not systematically provided preventive treatment during the study period. Furthermore, because both the numerators and denominators in our calculations were provided by

TB notification and census data, loss to follow-up and right-censoring were not concerns in our study, as they are in observational cohort studies.

This manuscript used data from a large, diverse migrant cohort in a twenty-first century low-incidence setting to provide insights into the natural history of TB. To our knowledge this is the first time that TB rates among migrant populations have been used to provide estimates of TB reactivation rates over time, by age and gender, although this approach could easily be adopted by others with access to census and TB notification data. Intelligently directed policy is required to prevent TB and this data will be important to ensure that new TB control strategies can be appropriately targeted at those who are at greatest of TB reactivation, working towards both TB elimination and promoting the long-term health of migrants.

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Conflicts of Interest

The authors declare no competing interests.

KDD No conflict

JMT No conflict

PJD No conflict

RMGJH No conflict

JTD No conflict

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Table 1 Characteristics of TB cases among Australian migrants and corresponding migrant study populations aggregated across census years 2006, 2011 and 2016.

	TB cases*		Aggregated number estimated to have latent TB		Aggregated total migrant population	
	n	(%)	n	(%)	n	(%)
Total	3,246	(100.0)	2,084,087	(100.0)	14,671,064	(100.0)
Female	1,505	(46.4)	1,123,506	(53.9)	7,511,367	(51.2)
Male	1,741	(53.6)	960,581	(46.1)	7,159,697	(48.8)
<65 years	2,758	(85.0)	1,621,841	(77.8)	11,943,721	(81.4)
≥65 years	488	(15.0)	462,246	(22.2)	2,727,343	(18.6)
Country of birth						
China	247	(7.6)	257,872	(12.4)	1,075,897	(7.3)
India	665	(20.5)	229,023	(11.0)	866,356	(5.9)
Vietnam	333	(10.3)	257,645	(12.4)	533,355	(3.6)
Philippines	297	(9.1)	234,102	(11.2)	504,203	(3.4)

Definition of abbreviations: TB= tuberculosis
*Excluding cases born in Papua New Guinea and notified in Queensland.

Table 2 Post-migration reactivation rates of cohorts by age at migration (rows) over various time periods from migration (columns) for all migrants, females and males.

Age group at migration (years)	Average annual TB reactivation rates per 100,000 (UI)									
	All									
	< 5 years		5 - 10 years		10 - 20 years		20 - 40 years		40 - 60 years	
0-14	420	(300-570)	180	(110-290)	250	(150-380)	90	(40-210)	60	(10-280)
15-24	620	(520-720)	260	(200-340)	100	(60-160)	50	(30-110)	40	(10-170)
25-34	400	(320-480)	170	(120-230)	90	(50-140)	50	(30-110)	50	(20-200)
35-54	220	(160-310)	90	(60-140)	80	(40-130)	90	(50-180)	120	(40-450)
55-64	340	(200-570)	110	(40-240)	170	(90-350)	220	(120-450)		
≥65	420	(230-750)	320	(150-660)	330	(170-660)	280	(100-730)		
	Females									
	< 5 years		5 - 10 years		10 - 20 years		20 - 40 years		40 - 60 years	
0-14	460	(300-690)	210	(110-360)	200	(110-360)	110	(40-270)	70	(10-380)
15-24	570	(460-690)	250	(180-350)	80	(40-140)	30	(10-80)	30	(10-140)
25-34	370	(280-460)	180	(120-250)	80	(50-140)	40	(20-90)	40	(10-170)
35-54	170	(110-240)	70	(40-130)	60	(30-110)	80	(40-160)	80	(20-370)
55-64	270	(140-490)	80	(20-220)	130	(60-290)	150	(70-340)		
≥65	320	(150-660)	280	(110-670)	180	(70-450)	90	(10-450)		
	Males									
	< 5 years		5 - 10 years		10 - 20 years		20 - 40 years		40 - 60 years	
0-14	370	(230-570)	160	(80-300)	290	(160-480)	70	(20-190)	50	(10-290)
15-24	660	(540-800)	270	(200-370)	130	(70-210)	70	(30-170)	50	(10-240)
25-34	440	(340-550)	170	(110-240)	90	(50-160)	70	(30-150)	60	(20-270)
35-54	290	(200-410)	110	(60-180)	100	(50-180)	110	(60-230)	180	(50-740)
55-64	450	(240-830)	150	(50-400)	250	(120-560)	370	(190-820)		
≥65	540	(270-1050)	370	(150-870)	530	(270-1150)	620	(210-1760)		

Definition of abbreviations: TB= tuberculosis; UI=uncertainty intervals

Figure Legends

Figure 1 Panels a, b and c show TB notification rates (taking the whole migrant population as the denominator) a) by gender and time from migration in all migrants, b) by gender and age group in all migrants, and c) by gender and age group in migrants who arrived more than five years prior to each census. Panels d, e and f show post-migration TB reactivation rates (using migrants estimated to have LTBI as the denominator) d) by gender and time from migration in all migrants, e) by gender and age group in all migrants (truncated value: 0-4 years, 2780 per 100,000), and f) by gender and age group in migrants who arrived more than five years prior to each census. Error bars show uncertainty intervals.

Figure 2 Post-migration reactivation rates in Australian migrant cohorts by age at migration (horizontal panels) and age at disease onset, with uncertainty intervals. Truncated value: 0-4 year age group migrating from 0-4 years of age, 2,776 per 100,000. Error bars show uncertainty intervals.

Figure 3 Post-migration reactivation rates of pulmonary TB by ten year age groups in all migrants (left panel) and in those who migrated more than five years prior to each census (right panel). Error bars show uncertainty