1 **Estimating long-term tuberculosis reactivation rates in Australian**

2 **migrants**

3 *Katie D. Dale[1]*, James M. Trauer[1,2], Peter J. Dodd[3], Rein M.G.J. Houben[4,5], Justin T. Denholm.[1,6]

4 [1] Victorian Tuberculosis Program, Melbourne Health, Victoria, Australia

5 [2] School of Public Health and Preventive Medicine, Monash University, Victoria, Australia

6 [3] School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom

7 [4] TB Modelling Group, TB Centre, London School of Hygiene and Tropical Medicine, London, United

8 Kingdom

9 [5] Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical

10 Medicine, London, United Kingdom

11 [6] Department of Microbiology and Immunology, The University of Melbourne, Victoria, Australia

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15 Corresponding author:

16   Katie Dale

17   Victorian Tuberculosis Program, Peter Doherty Institute

18   Level 5, 792 Elizabeth St

19   Melbourne VIC 3000

20   Phone: +61 417 543 713

21   Fax: 8344 0781

22   Email: katie.dale@mh.org.au

23   Alternate corresponding author:

24   Justin Denholm

25   Victorian Tuberculosis Program, Peter Doherty Institute

26   Level 5, 792 Elizabeth St

27   Melbourne VIC 3000

28   Phone: +61 407 453 950

29   Fax: 8344 0781

30   Email: justin.denholm@mh.org.au

31   Summary:

32   We estimated TB reactivation rates in Australian migrants by combining time and country-specific

33   infection estimates with census and notification data. Post-migration reactivation rates declined

34   over time from migration, and also appeared to increase during youth (aged 15-24 years) and old-

35   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

83   studies have yet considered TB rates over time in migrant cohorts whilst accounting for all of these

84   predictors of infection risk.

85   We previously estimated the prevalence of LTBI in Australian migrants using country-specific data on

86   annual risk of TB infection (ARTI) and applying them to national census data by country of birth, age

87   and year of migration [12]. Here we combine these estimates with data on Australian TB

88   notifications in migrants to better understand how TB reactivation rates vary with time since

89   migration, as well as with gender and age.

Methods

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Census data

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92   Australian population data from the 2006, 2011 and 2016 censuses were exported from the

93   Australian Bureau of Statistics (ABS) Table Builder [13] by country of birth, sex, age and year of

94   migration. Residents without a designated country of birth or year of migration were excluded from

95   analysis.

Notification data

96

97   Australian TB case data were obtained for each census year from Australian National Notifiable

98   Diseases Surveillance System data (accessed 23/02/2018) by year and state of notification, country

99   of birth, age, sex, site of disease and year of migration. In Australia a confirmed case of TB requires

100   culture or polymerase chain reaction confirmation of *Mtb*, or diagnosis by a clinician experienced in

101   TB management, including clinical follow-up to ensure a consistent clinical course [14].

Annual risks of infection and reactivation rates

102

103   The methods used to estimate Australian LTBI prevalence in the study years have been previously

104   described [12, 15]. Briefly, for each of 168 countries and for each year from 1934 to 2014, simulated

105   ARTI trajectories were estimated using data from tuberculin skin test (TST) surveys and/or WHO

106 Global TB Programme prevalence estimates (1990–2014), which were adjusted based on a revised

107 Styblo ratio [15]. The prevalence of LTBI was estimated for each population cohort by country of

108 birth, age and year of migration. In contrast to previous work, in this study we assumed that

109 infection was acquired premigration and so assumed that the ARTI in Australia was zero.

110 Furthermore, gender was a variable of interest in this analysis, although the prevalence of LTBI in

111 arrival cohorts was assumed to be equal for each gender. Data on all Australian TB notifications from

112 1st January to 31st December in 2006, 2011 and 2016 were merged with the relevant census and LTBI

113 prevalence data. Representative census groups were added for any unmatched notifications.

114 TB case numbers, the number estimated to have LTBI and total population numbers were

115 aggregated over each cohort considered. TB notification rates were calculated as the number of TB

116 notifications divided by the total population, with 95% confidence intervals calculated using the

117 Poisson exact test. Post-migration reactivation rates were calculated as the annual number of TB

118 cases in each population group divided by the median estimated prevalence of LTBI. Lower and

119 upper uncertainty intervals (UI) are given by the upper and lower 95% confidence intervals of the

120 Poisson exact test using the number of TB cases and the 75th and 25th percentiles of the LTBI

121 prevalence estimates, respectively.

122 We use the term "reactivation" throughout to refer to all TB cases that occurred post-migration,

123 although we acknowledge that an unknown number of TB cases may have been due to primary

124 progression following recent infection acquired premigration, in Australia or during overseas travel.

125 We use the term "migrant" to refer to anyone born outside Australia.

126 Australia's Torres Strait Islands are close to Papua New Guinea (PNG) and The Torres Strait Treaty

127 allows free movement of people between the countries for traditional activities [16]. Some PNG

128 residents seek medical care in Australia and those with TB were included in Australia's notification

129 data during the study years [16]. Because these individuals were not Australian residents we

130   excluded all TB cases notified in Queensland and born in PNG from our analysis, recognising that this

131   also would have excluded TB cases in PNG-born Queensland residents.

132   Sensitivity analyses

133   In LTBI prevalence calculations we assumed that ARTI was zero after migration. We assessed the

134   impact of this assumption by recalculating reactivation rates assuming the risk of infection continued

135   post-migration using Australian ARTI estimates [12].

136   We used 1934 ARTI estimates for all years prior to 1934. To ensure this assumption did not have any

137   appreciable effect on our conclusions, we illustrate reactivation rates only in those migrants born in

138   or after 1934.

139   We also assessed the likely impact of missing census data. To account for non-responding dwellings

140   the ABS post-enumeration survey provides undercount adjustment factors with associated standard

141   errors for census groups by age-group and sex and for selected countries of birth by sex (without

142   year of migration information) [17-19]. We applied these factors to migrant cohort size estimates to

143   assess the impact that excluding census non-respondents may have had on reactivation rates. The

144   ABS applies perturbation to TableBuilder data to manage disclosure risk; we examined its effect by

145   re-extracting data by fewer and grouped variables, applying grouped ARTI risks, and recalculating

146   reactivation rates.

147   Year of migration was missing for some census and TB case data and we explored the possible

148   impact of this on results using the predictive mean matching method to impute these values using

149   the MICE package [20] and R, version 3.4.4 (Boston, MA).

150   Ethics statement

151   Data for this project was collected under relevant Australian jurisdictional public health legislation.

152   Relevant database managers authorised the use of non-identifiable census and notification data.

153   According to the rules of our institutions, additional approval from an Institutional Ethics Committee

154   was not required.

Results

156   The characteristics of the study cohort are presented in Table 1 and are disaggregated by census

157   year in Table S1, together with details of missing data. Australian residents born in India, China, the

158   Philippines and Vietnam made up the greatest number estimated to have LTBI in the census years

159   (Table 1).

160   TB notification rates

161   The TB notification rates of migrants arriving in Australia in 2006, 2011 and 2016 were

162   114/100,000/year, 91/100,000/year and 82/100,000/year, respectively. Rates decreased with

163   increasing time from migration, were higher in males than females and showed some age

164   dependency (Figure 1a /b/c).

165   TB notification rates within the first five years after migration were broadly equivalent to, or lower

166   than, the World Health Organization (WHO) birth country TB incidence estimates in each census

167   year, and rates were largely lower again with increasing time from migration, but remained higher

168   than the Australian TB notification rates, even in cohorts that had migrated more than twenty years

169   earlier (Figure S1).

170   Reactivation rates

171   Of all Australian migrants estimated to have LTBI, the median TB reactivation rates were lower in

172   cohorts with increasing time from migration to at least 20 years post-migration, after which it was

173   uncertain whether further declines occurred (Figure 1d), with rates apparently stable around 60-

174   70/100,000/year. In the first five years after migration, the average annual reactivation rate was

175   400/100,000 (UI 320-480). From five-to-ten, ten-to-twenty, twenty-to-forty and forty-to-sixty years

176   from migration rates were 170 (UI: 130-220), 110 (UI: 70-160), 70 (UI: 40-140) and 60 (UI: 20-190),

177   respectively. However, reactivation rates also showed dependency on both age and gender (Figure

178   1e and Figure S2), such that rates varied depending on age at arrival, gender and time since

179   migration (Figure 1e/f, Table 2 and Table S2).

180   There was little difference in these patterns over the three census years, although the rates in 2016

181   appeared slightly lower than the previous years (Figure S2).

182   Figure 2 presents post-migration reactivation rates by age at migration and age. The highest

183   reactivation rates soon after migration were seen in young children, youth (15 to 24 years of age)

184   and the elderly. Regardless of the age at migration, rates decreased in cohorts with increasing time

185   from migration, although greater uncertainty was seen with increasing time from migration and in

186   cohorts that had migrated under five or over 69 years of age. On the background of otherwise

187   declining reactivation rates with time from migration, there also appeared to be increases in youth

188   and those aged 70 years and over (Figure 2). Results further disaggregated by gender are shown in

189   Figure S3, showing higher reactivation rates in males in some cohorts, particularly in the elderly.

190   Similar trends were observed when considering pulmonary and extrapulmonary TB separately

191   (Figure S4 and Figure 3).

192   When considering age-matched cohorts with LTBI from different countries of birth, the greatest

193   variation in reactivation rates was seen in the first years after migration, while rates progressively

194   converged with time from migration (Figure S5).

195   Sensitivity analysis

196   All sensitivity analyses resulted in negligible effects on reactivation rates and main findings. Applying

197   Australian ARTI estimates following migration marginally lowered rates among cohorts who

198   migrated >40 years ago (Figure S6); accounting for census non-respondents by applying the ABS

199   post-enumeration survey undercounts marginally changed absolute reactivation rate estimates

200   (typically by no more than 4.3%) (Figure S7); imputation of missing years of migration had a

201   negligible effect (unpublished data); ABS data re-extraction using grouped variables marginally

202   reduced rates, particularly in the elderly (Figure S8) and excluding migrants born before 1933 also

203   had a negligible effect on overall patterns and main findings (Figure S9).

204   **Discussion**

205   In our simulated cohort of Australian migrants with LTBI, TB reactivation rates appeared to be

206   dependent on both time from migration and age, with lower rates seen with increasing time from

207   migration and possible increases in rates in those aged 70 years and during youth. Although these

208   trends are consistent with existing observations [9, 21-25], to our knowledge, this is the first time all

209   these phenomena have been demonstrated in a single study, and the first study to use estimated

210   LTBI prevalence among migrant populations to provide insights into the natural history of TB. While

211   Australian migrant populations are highly heterogeneous and the reasons for TB reactivation may be

212   multi-factorial and complex, *Mtb* infection is the only absolute prerequisite for reactivation, and our

213   study demonstrates that taking into account infection risk can clarify average reactivation risk in

214   such heterogeneous populations. Furthermore, the quantification of post-migration reactivation

215   rates will be useful in the planning of targeted TB control strategies.

216   Our results confirmed that the passing of time from migration had an impact on reactivation rates.

217   Lower rates were observed in cohorts that had migrated longer ago, whether comparing across birth

218   cohorts or cohorts who had all migrated at a similar age, and long term rates were consistent with

219   reactivation rate estimates made by Shea *et al.* 2014 in US migrant cohorts [23]. In our low-incidence

220   setting the lower rates seen with increasing time from migration is likely to indicate that disease risk

221   declines with increasing time from infection; and this observation has also recently been made

222   regarding US migrants [22]. Further, with TB reactivation rates highest soon after infection,

223   differences in the proportion of cohorts that had been recently or remotely infected premigration is

224   likely to explain the varying reactivation rates seen in migrant cohorts from different countries in the

225   early years following migration. This effect may also explain the slightly lower rates seen in the latest

226   census year, because TB incidence in many of the countries where recent migrants were born has

227   declined slightly over time. Additional explanations for these observations could include different

228   off-shore premigration TB detection practices, or changes in the migrant mix from countries that

229   may have influenced their premigration infection or progression risk. Post-migration reactivation

230   rates may also partially reflect the different living conditions that many new migrants experience

231   [21].

232   In addition to time, there were also indications in our results that the risk of progression may differ

233   along life course, with higher reactivation rates in elderly cohorts and youth when compared to

234   younger cohorts that had migrated at a similar age. These observations have been made before [9,

235   25-31], and the pattern of pulmonary TB reactivation rates we observed by age post-migration

236   resembles that of a study in Ontario, Canada that compared TST-survey data from 1958 to 1960 to

237   pulmonary TB cases across the same region in 1962 (Figure S10) [21]. Further evidence that

238   reactivation rates may increase into old age can also be observed in other studies [32, 33], including

239   birth cohort studies [30, 31] and a recent study in Canadian migrants [9], and plausible reasons may

240   include weakened immune status and increasing prevalence of comorbidities associated with old

241   age [34-36]. Previous studies have also observed a period of increased reactivation risk during youth

242   [25-29], but whether these increases are due to reactivation of quiescent infections, or an increased

243   risk of reinfection is debateable. Our study provides additional evidence for this debate from a low-

244   incidence setting, but we also cannot exclude that an increased risk of reinfection into youth led to

245   the few cases that caused these observations in our setting. This is because of the following

246   important assumption/limitation of our study.

247   Our study design assumes that all TB cases in the study cohort arose from reactivation of latent

248   infection acquired premigration. However, some will have resulted from infection acquired post-

249   migration during either local transmission [4] or travel overseas, or from relapsed TB cases [37].

250   Previously published studies in Victoria support low rates of local transmission (4.2% of culture-

251   confirmed TB cases from 2003-2010 "likely" to be due to local transmission) [4] and relapse [37], but

252   genotypic and epidemiological information were not available for all Australian TB cases. Because

253   we could not exclude cases due to local transmission, overseas travel or relapse, some presented

254   reactivation rates will overestimate the contribution of infection that was acquired premigration.

255   National genotyping studies and studies that refine estimates of travel-associated risk by age will be

256   valuable in the future, and will help to clarify the effect of age on reactivation rates.

257   A discussion of the limitations of the original modelled LTBI prevalences can be found in our previous

258   publications [12, 15]. Particularly pertinent to the current results is that we uniformly applied ARTI

259   estimates by country of birth, year and gender, but acknowledge that infection risk is likely to vary

260   within countries between populations and by age and gender [21, 38]. For example, while we

261   observed higher reactivation rates in males, which is in line with wider observations of TB incidence

262   [39], the relative importance of differential infection or progression risk or ability to clear infection

263   [24], in our study cohort is unknown.

264   Our study also assumed that untreated LTBI persists lifelong. However, there is evidence to suggest

265   that LTBI may naturally resolve over time (e.g. TST reversion) [21, 40, 41], and, if so, our estimates

266   may increasingly underestimate rates among contemporary TST reactors with time. Additionally,

267   data on comorbidities such as HIV or diabetes were not considered, limiting generalisability of our

268   results to settings with a different frequency of risk factors.

269   Despite the limitations, our method also has a number of important strengths. In contrast to

270   observational studies among TB contacts, which usually have small samples, seldom have more than

271   two years of follow up, and are complicated by the provision of preventive treatment, an estimated

272   two million migrants were included in our analysis, time since migration spanned decades, and

273   migrants were not systematically provided preventive treatment during the study period.

274   Furthermore, because both the numerators and denominators in our calculations were provided by

275 TB notification and census data, loss to follow-up and right-censoring were not concerns in our

276 study, as they are in observational cohort studies.

277 This manuscript used data from a large, diverse migrant cohort in a twenty-first century low-

278 incidence setting to provide insights into the natural history of TB. To our knowledge this is the first

279 time that TB rates among migrant populations have been used to provide estimates of TB

280 reactivation rates over time, by age and gender, although this approach could easily be adopted by

281 others with access to census and TB notification data. Intelligently directed policy is required to

282 prevent TB and this data will be important to ensure that new TB control strategies can be

283 appropriately targeted at those who are at greatest of TB reactivation, working towards both TB

284 elimination and promoting the long-term health of migrants.

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298   interpretation, or writing of the report. The corresponding author had full access to all the data and

299   had final responsibility for the decision to submit for publication.

300   **Conflicts of Interest**

301   The authors declare no competing interests.

302   KDD No conflict

303   JMT No conflict

304   PJD No conflict

305   RMGJH No conflict

306   JTD No conflict

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402 **Table 1 Characteristics of TB cases among Australian migrants and corresponding migrant study populations aggregated**

403 **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.						

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405 **Table 2 Post-migration reactivation rates of cohorts by age at migration (rows) over various time periods from migration**

406 **(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

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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