

1 **Estimating long-term tuberculosis reactivation rates in Australian** 2 **migrants**

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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.

36 **Abstract**

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

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

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

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

57

58 Introduction

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

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

77 Studies that have reported TB rates among migrants over time since migration to low-incidence
78 settings have often found the greatest risk of disease in the first years after migration [6-9]. While
79 some studies have shown decreasing TB rates beyond this period [6, 8], in other cohorts rates did
80 not decrease uniformly over time [7, 10, 11]. Such variation in findings may relate to the
81 heterogeneity of the migrant populations studied with regards to historical TB burden and time in
82 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.

90 **Methods**

91 **Census data**

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.

96 **Notification data**

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].

102 **Annual risks of infection and reactivation rates**

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.

155 **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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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

307

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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.						

404

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

407

408

409 **Figure Legends**

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

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

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