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

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14 Running title (<41 character and spaces): Tuberculosis reactivation in 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 1<sup>st</sup> January to 31<sup>st</sup> 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 75<sup>th</sup> and 25<sup>th</sup> 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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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

307

## 308 References

- 309 1. Lillebaek T, Dirksen A, Baess I, Strunge B, Thomsen VO, Andersen AB. Molecular evidence of  
310 endogenous reactivation of Mycobacterium tuberculosis after 33 years of latent infection. *J*  
311 *Infect Dis* **2002**; 185(3): 401-4.
- 312 2. Department of Health & Human Services. Management, control and prevention of  
313 tuberculosis Guidelines for health care providers, **2015**.
- 314 3. Flynn MG, Brown LK. Treatment of latent tuberculosis in migrants to Victoria. *Commun Dis*  
315 *Intell Q Rep* **2015**; 39(4): E578-83.
- 316 4. Globan M, Lavender C, Leslie D, et al. Molecular epidemiology of tuberculosis in Victoria,  
317 Australia, reveals low level of transmission. *Int J Tuberc Lung Dis* **2016**; 20(5): 652-8.
- 318 5. Toms C, Stapledon R, Waring J, Douglas P. Tuberculosis notifications in Australia, 2012 and  
319 2013. *Commun Dis Intell* **2015**; 38(4).
- 320 6. McBryde ES, Denholm JT. Risk of active tuberculosis in immigrants: effects of age, region of  
321 origin and time since arrival in a low-exposure setting. *Med J Aust* **2012**; 197(8): 458-61.
- 322 7. Creatore MI, Lam M, Wobeser WL. Patterns of tuberculosis risk over time among recent  
323 immigrants to Ontario, Canada. *Int J Tuberc Lung Dis* **2005**; 9(6): 667-72.
- 324 8. Cain KP, Benoit SR, Winston CA, Mac Kenzie WR. Tuberculosis among foreign-born persons  
325 in the United States. *JAMA* **2008**; 300(4): 405-12.
- 326 9. Ronald LA, Campbell JR, Balshaw RF, et al. Demographic predictors of active tuberculosis in  
327 people migrating to British Columbia, Canada: a retrospective cohort study. *CMAJ* **2018**;  
328 190(8): E209-E16.
- 329 10. Walter ND, Painter J, Parker M, et al. Persistent latent tuberculosis reactivation risk in United  
330 States immigrants. *Am J Respir Crit Care Med* **2014**; 189(1): 88-95.
- 331 11. Vos AM, Meima A, Verver S, et al. High incidence of pulmonary tuberculosis persists a  
332 decade after immigration, The Netherlands. *Emerg Infect Dis* **2004**; 10(4): 736-9.
- 333 12. Dale KD, Trauer JM, Dodd PJ, Houben RMGJ, Denholm JT. Estimating the prevalence of latent  
334 tuberculosis in a low incidence setting: Australia. *Eur Respir J* **2018**; 52(6).
- 335 13. Australian Bureau of Statistics. TableBuilder. Available at:  
336 <http://www.abs.gov.au/websitedbs/censushome.nsf/home/tablebuilder>. Accessed 12 July.
- 337 14. Communicable Diseases Network Australia (CDNA). Tuberculosis case definition. Available  
338 at: [http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-](http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_tb.htm)  
339 [casedefs-cd\\_tb.htm](http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_tb.htm). Accessed 27 February 2017.
- 340 15. Houben RM, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation  
341 Using Mathematical Modelling. *PLoS Med* **2016**; 13(10): e1002152.
- 342 16. Australian Government Department of Foreign Affairs and Trade. Torres Strait: The Torres  
343 Strait Treaty. Available at: [https://dfat.gov.au/geo/torres-strait/Pages/the-torres-strait-](https://dfat.gov.au/geo/torres-strait/Pages/the-torres-strait-treaty.aspx)  
344 [treaty.aspx](https://dfat.gov.au/geo/torres-strait/Pages/the-torres-strait-treaty.aspx). Accessed 18 October 2018.
- 345 17. Harding S, Jackson Pulver L, McDonald P, Morrison P, Trewin D, Voss A. Report on the quality  
346 of 2016 Census data.: Census Independent Assurance Panel to the Australian Statistician,  
347 **2017**.

- 348 18. Australian Bureau of Statistics. 2940.0 - Census of population and housing - details of  
349 undercount, Australia. Canberra, **2012**.
- 350 19. Australian Bureau of Statistics. 2940.0 - Census of Population and housing - details of  
351 undercount. Canberra: Australian Bureau of Statistics, **2007**.
- 352 20. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations  
353 in R. *Journal of Statistical Software* **2011**; 45(3): 1-67.
- 354 21. Grzybowski S, Allen EA. The Challenge of Tuberculosis in Decline. A Study Based on the  
355 Epidemiology of Tuberculosis in Ontario, Canada. *Am Rev Respir Dis* **1964**; 90: 707-20.
- 356 22. Menzies NA, Hill AN, Cohen T, Salomon JA. The impact of migration on tuberculosis in the  
357 United States. *Int J Tuberc Lung Dis* **2018**; 22(12): 1392-403.
- 358 23. Shea KM, Kammerer JS, Winston CA, Navin TR, Horsburgh CR, Jr. Estimated rate of  
359 reactivation of latent tuberculosis infection in the United States, overall and by population  
360 subgroup. *Am J Epidemiol* **2014**; 179(2): 216-25.
- 361 24. Wiker HG, Mustafa T, Bjune GA, Harboe M. Evidence for waning of latency in a cohort study  
362 of tuberculosis. *BMC Infect Dis* **2010**; 10: 37.
- 363 25. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in  
364 childhood and adolescence. *Am J Epidemiol* **1974**; 99(2): 131-8.
- 365 26. Leung CC, Yew WW, Au KF, et al. A strong tuberculin reaction in primary school children  
366 predicts tuberculosis in adolescence. *Pediatr Infect Dis J* **2012**; 31(2): 150-3.
- 367 27. Pope AS, Sartwell PE, Zacks D. Development of Tuberculosis in Infected Children. *Am J Public  
368 Health Nations Health* **1939**; 29(12): 1318-25.
- 369 28. Myers JA, Bearman JE, Dixon HG. Natural History of Tuberculosis in the Human Body. VIII.  
370 Prognosis among Tuberculin Reactor Girls and Boys of Thirteen to Seventeen Years. *Am Rev  
371 Respir Dis* **1965**; 91(6): 896-908.
- 372 29. Myers JA, Bearman JE, Dixon HG. The Natural History of Tuberculosis in the Human Body. V.  
373 Prognosis among Tuberculin-Reactor Children from Birth to Five Years of Age. *Am Rev Respir  
374 Dis* **1963**; 87(3; Pt 1): 354-69.
- 375 30. Tocque K, Bellis MA, Tam CM, et al. Long-term trends in tuberculosis. Comparison of age-  
376 cohort data between Hong Kong and England and Wales. *Am J Respir Crit Care Med* **1998**;  
377 158(2): 484-8.
- 378 31. Haro AS. Cohort approach in tuberculosis surveillance: comparison of the situation in  
379 Sweden and Finland. *Tuber Lung Dis* **1994**; 75(4): 271-82.
- 380 32. Horsburgh CR, O'Donnell M, Chamblee S, et al. Revisiting Rates of Reactivation Tuberculosis.  
381 *Am J Respir Crit Care Med* **2010**; 182(3): 420-5.
- 382 33. Stead WW, Lofgren JP. Does the risk of tuberculosis increase in old age? *J Infect Dis* **1983**;  
383 147(5): 951-5.
- 384 34. Stead WW, Dutt AK. Tuberculosis in the elderly. *Semin Respir Infect* **1989**; 4(3): 189-97.
- 385 35. Donald PR, Marais BJ, Barry CE. Age and the epidemiology and pathogenesis of tuberculosis.  
386 *The Lancet* **2010**; 375(9729): 1852-4.
- 387 36. Rajagopalan S. Tuberculosis in Older Adults. *Clin Geriatr Med* **2016**; 32(3): 479-91.
- 388 37. Dale KD, Globan M, Tay EL, Trauer JM, Trevan PG, Denholm JT. Recurrence of tuberculosis in  
389 a low-incidence setting without directly observed treatment: Victoria, Australia, 2002-2014.  
390 *Int J Tuberc Lung Dis* **2017**; 21(5): 550-5.

- 391 38. Gedde-Dahl T. Tuberculous infection in the light of tuberculin matriculation. *Am J Hyg* **1952**;  
392 56(2): 139-214.
- 393 39. Horton KC, MacPherson P, Houben RM, White RG, Corbett EL. Sex Differences in  
394 Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic  
395 Review and Meta-analysis. *PLoS Med* **2016**; 13(9): e1002119.
- 396 40. Ferebee S. Controlled chemoprophylaxis trials in tuberculosis. A general review. *Bibl Tuberc*  
397 **1970**; 26: 28-106.
- 398 41. Daniels M, Ridehalgh F, Springett VH, Hall IM. Tuberculosis in young adults: report on the  
399 Proffit Tuberculosis Survey, 1935-1944. London: H.K. Lewis, **1948**.
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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)		
<b>Females</b>										
	< 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)		
<b>Males</b>										
	< 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