Appendix (unedited, as supplied by the authors)

Appendix

Sensitivity analysis

There was a maximum of 20 years prior to entry into the study observation period, with a mean of 5.5 and a median of 4 years. The method of survival analysis used in this study takes this into account provided the individuals survive to the observation period. However, if attrition takes place and is not observed (left-truncated data) the resulting incident rate is an estimate necessitating some assumptions (see Lawless, J. F. (1982)[1], for a description of left censored data).

We tested the sensitivity of the outcome results to the study assumptions. The first assumption that was relaxed was that the denominator (all permanent residents to Victoria arriving between 1975 and 2007 inclusive) would undergo attrition at a rate similar to Australian death rates. This assumption could either under or over-estimate the denominator. It could under-estimate the denominator because, studies of immigrants find that in fact the risk of death adjusted for age and sex is actually up to 15% lower for immigrants than for Australian born people.[2] Additionally, net migration into the state is also possible. It could over-estimate the at-risk group because death rates may be higher in immigrants in this particular cohort, or there may be a net migration out of Victoria by these immigrants either interstate or overseas or they may have acquired TB prior to the observation period (reducing their risk of presenting within the observation period).

We therefore re-examined the dataset under two extreme assumptions. Our first sensitivity test was to assume that there was no death or attrition of this cohort at all. Our second sensitivity test was to assume that there was a 3% attrition rate per year. To put this into the context of the study, this rate of attrition is approximately the death rate of a 79 year old Australian woman in the year 2000. Hence both of the above sensitivity tests are likely to lie well outside the true range of possibilities.

Figure 1 shows the results with the effect of no attrition not markedly different from the baseline assumption. With the 3% attrition assumption, the effect becomes substantial in the over 60 age groups. Figure 1 illustrates that the estimates of incidence in the elderly are much more sensitive to the assumptions of the model than estimates in the younger age groups, as one would expect when assumptions are about death and attrition rates. It also shows that the lower estimates of incidence in the elderly (blue bars) are not far from those of the main paper (red bars), whereas the upper estimates of incidence are considerably higher. Finally, figure 1 shows that regardless of the assumptions the qualitative finding that there is a marked second peak of incidence in the elderly remains.

Appendix Figure 1: Estimated risk of tuberculosis per 100,000 years under three assumptions a. no deaths or attrition (blue) b. baseline assumption, Australian death rate (red) c. Australian death rate plus 3% reduction in immigrant population per year (green)

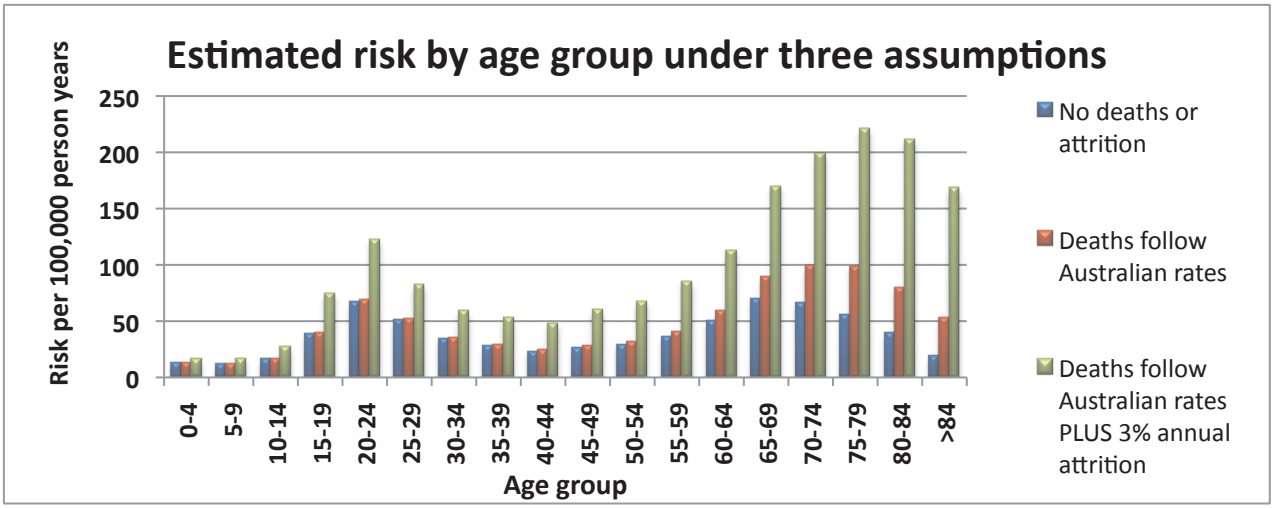
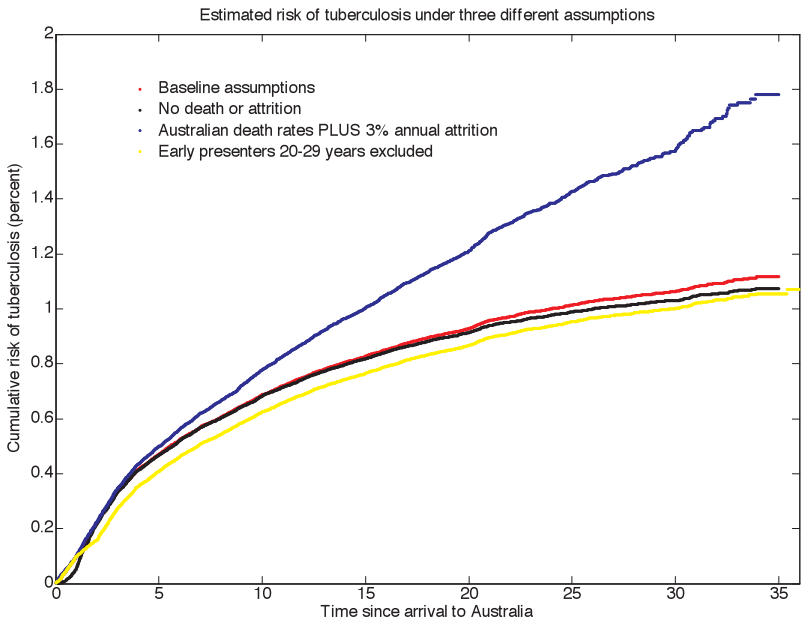


Figure 2 shows the effect of these different assumptions on the cumulative risk of active tuberculosis as a function of time since arrival. The estimates of incidence become sensitive to assumptions regarding death rates, beyond about 10 years following immigration. Again this is predictable, since attrition rates are cumulative and age-related. As time since arrival increases, the differences in the denominators (number in arrival cohort) under the three assumptions become more marked.

Appendix Figure 2: Cumulative risk of tuberculosis following immigrant arrival into Australia under four different assumptions.



Regarding the notified cases of active tuberculosis; missed diagnoses are unlikely unless people return home, move interstate or die before their tuberculosis is diagnosed. Excess diagnoses may occur in the case when students-planning to return and never registered as permanent residents - are included in the notified cases.

The second component of the sensitivity analysis assessed the potential impact of student/temporary visitor cases of incident tuberculosis on the analysis. We found 200 cases (3.7%) notified and included in the study were from individuals who arrived within 2 years of the diagnosis and who were aged 20-29 years. A proportion of these could have been students. We excluded all of these people from the study and re-examined the data. The effect of excluding all possible student cases in these age groups was to reduce the incidence rate from 69 to 58 per 100,000 person years in the 20-24 age-group and from 52 to 44 per 100,000 person years in the 25-29 age-group. Other age groups were unaffected. Hence there is an 18% reduction in incident rate if all immigrants of this age group who present within two years are excluded. This clearly overstates the number of incident cases that are temporary residents as it includes all immigrants. Figure 5 shows the effect of excluding all early presenters with TB on the cumulative risk curve. The yellow line tracks lower than the baseline assumptions because the number of notifications is reduced by 3.7%.

Factors affecting hazard of tuberculosis incidence

The hazard ratio for developing active tuberculosis by age and by region is given in Appendix Table 1. The hazard of tuberculosis is highest for Sub-Saharan Africa and South Asia with South East Asia also very high. This table is a multivariate analysis, suggesting that the age distribution and in particular the effect of much higher risk in the elderly is still present after region of origin is taken into consideration.

References

1. Lawless, J. F. *Statistical models and methods for lifetime data* 1982, Wiley and Sons Publishing.
2. Wahlqvist, M. L., I. Darmadi-Blackberry, et al. "Does diet matter for survival in long-lived cultures?" *Asia Pac J Clin Nutr* 2005; **14**(1): 2-6

Age group at entry	Hazard Ratio	P value	95% Confidence interval		
0-4	1	ref			
05-09	1.1	0.67	0.7	to	1.6
10-14	1.9	<0.001	1.4	to	2.7
15-19	5.1	<0.001	3.8	to	7.0
20-24	7.7	<0.001	5.7	to	10.4
25-29	5.0	<0.001	3.7	to	6.7
30-34	3.8	<0.001	2.8	to	5.2
35-39	3.6	<0.001	2.7	to	4.9
40-44	3.3	<0.001	2.4	to	4.5
45-49	4.2	<0.001	3.1	to	5.9
50-54	4.9	<0.001	3.5	to	6.9
55-59	6.3	<0.001	4.4	to	8.9
60-64	8.1	<0.001	5.8	to	11.5
65-69	13.0	<0.001	9.3	to	18.1
70-74	16.1	<0.001	11.4	to	22.8
75-79	17.7	<0.001	12.1	to	25.9
80-84	18.8	<0.001	12.0	to	29.5
>84	18.3	<0.001	10.7	to	31.3
Region					
Western & Northern Europe	1	ref			
Oceania excl Aus /NZ	15.6	<0.001	10.4	to	23.5
Southern and Eastern Europe	4.9	<0.001	3.4	to	7.2
Middle East & North Africa	12.0	<0.001	8.3	to	17.2
South East Asia	30.3	<0.001	21.6	to	42.6
North East Asia	14.8	<0.001	10.4	to	21.1
South Asia	40.6	<0.001	28.8	to	57.2
USA & Canada	2.7	<0.001	1.4	to	5.4
America excl USA/Can	3.7	<0.001	2.1	to	6.6
Sub-Saharan Africa	39.8	<0.001	28.1	to	56.5

Table 2: Multivariable model with region and age group modeled as categorical variables predicting hazard of tuberculosis. The reference group is the youngest age group (0-4y) and the *Oceania excluding Aus/NZ* region.