Estimating the prevalence of latent tuberculosis in a low incidence setting: Australia

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"Take home" message: Migration is a key driver of tuberculosis (TB) in many low incidence settings. Our method combines global TB infection estimates with migration data to provide useful insights into the prevalence of latent TB in a low-incidence setting, Australia.

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Summary

Migration is a key driver of tuberculosis (TB) in many low incidence settings, with the majority of TB cases attributed to reactivation of latent TB (LTBI) acquired overseas. A greater understanding of LTBI risk in heterogeneous migrant populations would aid health planning. We aimed to estimate the LTBI prevalence and distribution among local and overseas-born Australians.

Annual risks of tuberculosis infection estimates were applied to population cohorts (by country of birth, year of arrival and age) in Australian census data in 2006, 2011 and 2016.

Both the absolute number and proportion of Australian residents with LTBI increased – from 4.6% (IQR [interquartile range] 4.2-5.2%) in 2006 to 5.1% (IQR 4.7%-5.5%) in 2016 – due to the increasing proportion of the population born overseas (23.8% in 2006 to 28.3% in 2016). Of all residents estimated to have LTBI in 2016; 93.2% were overseas born, 21.6% were <35 years of age and 34.4% had migrated to Australia since 2007.

The overall prevalence of LTBI in Australia is low. Some residents, particularly migrants from high incidence settings, may have considerably higher risk of LTBI, and these findings allow for tailored public health interventions to reduce the risk and impact of future TB disease.

KEY WORDS: migration, epidemiologic methods, mathematical modelling

Introduction

In many low-incidence settings, most TB cases now occur among residents born in high-incidence countries and are attributed to reactivation of latent TB (LTBI) acquired overseas.[1] LTBI is asymptomatic and not infectious, but those with LTBI can be treated to reduce their future risk of reactivation TB,[2] and several low-incidence countries are now considering, or have implemented, screening and treatment for LTBI among high-risk recent immigrants.[3] It is essential that any strategy is well targetted to those at highest risk of active TB to ensure a favourable risk/benefit ratio for both society and individuals.[4 5] However, migrant populations can be very heterogeneous with regards to source country, age and time since migration, and most LTBI prevalence studies in migrant populations are limited to opportunistically selected groups with identifiable risk factors and demographic profiles that are unlikely to be generalisable to the entire migrant cohorts.[6]

In 2016, Houben and Dodd estimated the prevalence of global LTBI by estimating trends in annual risk of infection (ARTI) for 168 countries from 1934 to 2014.[7] In Australia, as in many low-incidence settings, immigration is a key driver of the burden of LTBI and rich data exist on immigration by country of origin, age and year. Therefore, the potential exists to combine estimated TB infection rates with domestic census data to quantify the LTBI burden and understand the effects of immigration.

We aimed to estimate the prevalence of LTBI in Australia, to describe its evolution over time and identify populations at greatest risk of infection. This is an important first step in identifying those populations that are at the highest risk of TB reactivation, and will inform future effective public health interventions towards TB elimination.

Methods

Australian census data

Australian population data from the 2006, 2011 and 2016 censuses were exported from the Australian Bureau of Statistics (ABS) Table Builder[8] by country of birth, age, year of arrival, State/Territory of residence and residence within State/Territory's capital city.

Residents categorised as "not stated", "inadequately described", "overseas visitor" or "at sea" in the census country of birth or year of arrival categories were excluded from analysis.[9]

Annual risk of infection

The methods used by Houben and Dodd 2016 to construct trends in annual risk of infection (ARTI) for 168 countries from 1934 to 2014 have been described in detail previously.[7] Briefly, for each country and for each year, 200 simulated ARTI trajectories were estimated using data from tuberculin skin test (TST) surveys, with sample size and mean age used to quantify uncertainty. Where TST surveys were unavailable, estimates of ARTI were obtained using a revised Styblo ratio that accounts for uncertainty.[10] The Styblo ratio relates the annual risk of infection and prevalence of smear-positive tuberculosis.[11 12] The prevalence of smear-positive TB was estimated using WHO Global TB Programme prevalence estimates (1990–2014)[13] and incorporating WHO assumptions regarding case detection rates and disease duration by HIV-status, as well as assumptions regarding the fraction of smear-positive disease by HIV status[14] and age-group.[15]

To increase precision for the six most common countries of birth in Australia (Australia, the United Kingdom, China, Vietnam, India and the Philippines), we simulated 5000 ARTI trajectories. To reflect characteristics relevant to transmission in Australia, the proportion of TB cases that were smear-positive was set to 21.5% based on the Australian average proportion from 2008 to 2013.[1 16-18] The ARTI estimate for 2014 was also applied to the years 2015 and 2016.

The risk of infection for each population cohort (by country of birth, age and year of arrival if overseas-born) in each census dataset was calculated by summing the relevant hazards (FOI=force of infection) for each year of residency in Australia and birth country (for overseas-born residents). To account for variation in birth dates and dates of migration across years (which were unknown), the hazards in birth years were halved, and in years of migration half the hazard for each of the birth country and Australia was used. This assumes that the average time of birth or migration of the cohort was the mid-point of the year of birth or migration. Hazards in census years were apportioned based on the census date. The total risk of infection (R) for each population group was then calculated as one minus the exponential of the cumulative FOIs experienced:

$$R = 1 - e^{\sum -(All\ FOIs)}$$ where FOI=force of infection

A full mathematical description of this method appears in the Appendices.

Ethics statement

Approval from a Human Research Ethics Committee was not required under the rules of our institutions.

RESULTS

LTBI in Australia

The number of Australians estimated to have LTBI increased over time from approximately 838,000 (IQR [interquartile range] 764,000-950,000) in 2006 to 1,084,000 (IQR 1,017,000-1,172,000) in 2016, with the percentage of Australians estimated to have LTBI increasing from 4.6% (IQR 4.2%-5.2%) in 2006 to 5.1% (IQR 4.7%-5.5%) in 2016 (Figure 1). Our results are estimates based on a Bayesian approach, and so computing P-values for comparisons between years was not appropriate, but the uncertainty intervals suggest no strong evidence of a trend.

Considering the Australian-born and overseas-born groups separately, the estimated LTBI percentages in the Australian-born residents were comparable in 2006 and 2016 (0.4% [IQR 0.3-0.9%] and 0.4% [IQR 0.3-0.7%]) and the percentage of overseas-born residents infected also changed little from 18.0% (IQR 16.7-19.6%) to 17.1% (IQR 16.2-18.1%). The reason why the proportions in the Australian-born and overseas-born subgroups changed little over time while there was a simultaneous increase in the proportion of all Australians estimated to have LTBI was because of the increasing proportion of the Australian population who were born overseas during the study years (23.8% in 2006 to 28.3% in 2016). The number of overseas-born residents estimated to have LTBI increased from 756,000 (IQR 699,000-822,000) in 2006 to 998,000 (IQR 943,000-1,058,000) in 2016.

With declining ARTI estimates in many countries worldwide, the percentage estimated to have LTBI increased with age in both Australian-born and overseas-born populations (Figure 2). Due to the age distribution of the populations (not shown) the largest number estimated to have LTBI were in the 35-64 year age-groups (Figure 2).

Among overseas-born residents, the number of persons with LTBI increased from 2006 to 2016 in all age groups, with the largest absolute increase in the 35-64 year and 15-34 year age groups, and percentage increases of 37.7%, 69.4%, 25.4% and 26.6% in the 0-14, 15-34, 35-64 and 65+ age groups respectively (Figure 2). The proportion of overseas-born residents estimated to have LTBI appeared to decrease marginally over time in all age-groups, except in the 35-64 year group, in which it changed little from 19.5% (IQR 17.9%-21.1%) in 2006 to 20.1% (IQR 18.7%-21.3%) in 2016 (Figure 2).

The average age of residents with LTBI appeared to decrease slightly from 51.9 years in 2006 to 50.7 years in 2016; increasing in the Australian-born population (50.5 years in 2006 to 52.4 years in 2016) and decreasing

in the overseas-born (52.0 years in 2006 to 50.6 years in 2016). The percentage of residents with LTBI under the age of 35 years increased from 17.4% in 2006 to 21.6% in 2016.

Overseas-born residents

In 2016, over 6.1 million Australian residents were born overseas in over 190 countries, constituting 28.3% of the Australian population. The increasing numbers of Australians born in high burden countries[19] over time is illustrated in Figure 3. Australian residents born in India, China, the Philippines and Vietnam made up the greatest number estimated to have LTBI in 2016; with the prevalence varying by age (Table 1 and Figure 4).

Overseas-born residents arriving 2007-2016

An estimated 15.4% of migrants arriving from 2007 until the census in 2016 had LTBI on arrival, with this group contributing 34.4% of all LTBI in Australia in 2016 and new migrants aged under 35 years contributing 16.3%.

Spatial distribution

The majority of persons with LTBI resided in major urban centres, particularly Greater Sydney and Greater Melbourne (Figure S1). LTBI prevalence increased in all regions from 2006 to 2016, most notably in the Northern Territory (1.7% in 2006 to 3.3% in 2016), Greater Perth (3.8 to 4.9%) and the Australian Capital Territory (2.8 to 3.9%). It is also possible to identify where those at greatest risk of TB infection live in urban areas, if census data provides this level of spatial detail (Figure S1).

Missing data

The percentage missing country of birth and/or year of arrival information in the 2006, 2011 and 2016 census data was 8.0%, 6.7% and 9.15% respectively. These census respondents were categorised as "not stated" and for a significant percentage (~70-80% depending on the year) the answers to most other census questions were similarly "not stated", suggesting they had been imputed by the ABS to account for non-responding dwellings.[9 20 21] The ABS post-enumeration survey data in the census years estimated the majority of non-responders to be Australian-born (e.g. 84.8% in 2016, which was calculated using the Tablebuilder census count and published net undercount rate of 8.1%).[9 20 21] and countries of birth of other non-responders were similarly distributed to census respondents in 2016.

DISCUSSION

Our method provided useful insights into the prevalence of LTBI in Australia; a low-incidence setting with high levels of migration. Both the prevalence and total number of people with LTBI in Australia rose from 2006 to 2016, with the highest proportions seen in major metropolitan areas. The increasing prevalence of LTBI can be attributed to increasing numbers of overseas-born residents from countries with a high burden of TB such as India, China and the Philippines. New arrivals were predominantly young adults and families,

such that an increasing proportion of those estimated to have LTBI during the study period were under 35 years of age. During this time, we found that around 15% of migrants to Australia had LTBI. However, due to high levels of migration from high-burden countries since the 1980s, the majority of those estimated to have LTBI in Australia in 2016 were over 35 years of age.

Our study highlighted that despite the increasing prevalence of LTBI in Australia, the prevalence is low (5.1% in 2016) and far lower than the estimated global burden of 23% in 2014.[7] Moreover, the proportion of residents estimated to have LTBI in the overseas-born population appeared to fall over time, due to the declining incidence of TB in the countries where most overseas-born residents were born (for example, India, and China).[19] How the prevalence of LTBI in Australia, and other similar low-incidence settings, change in the future will be influenced by rates of migration, age at migration, source countries, and how TB incidence in those source countries changes over time, in addition to the implementation and effectiveness of any additional TB control strategies locally.

Looking to the future, the addition of LTBI screening and treatment could be considered for migrant groups in Australia, as is done in several other low-incidence countries.[22] LTBI treatment is commonly limited to those aged under 35 years because the frequency of adverse effects increases with age,[23 24] although recent research has shown that shorter LTBI treatment regimens containing rifampicin have a significantly lower risk of hepatotoxicity, so recommendations for testing older age groups may expand into the future.[25] Our approach is able to quantify LTBI burden in sub-populations from low-burden countries, ensuring improved estimates of the pre-test probability of LTBI essential for predicting the efficiency of any proposed screening program. In addition, understanding LTBI distribution is helpful even where preventive therapy would not be indicated, and allows alternative interventions (such as community and healthcare worker education about TB disease) to be optimised. Migrants arriving from high-burden settings from 2007 to 2016 made up over 30% of all those with LTBI in Australia in 2016, and because recently arriving migrants are at higher risk of reactivating than those that have settled in Australia for longer [26] screening and treating this group may be beneficial. Quantifying this benefit will be a focus of future work, which will incorporate estimation of TB reactivation rates among sub-populations with LTBI. Given the significant uncertainty around rates of LTBI reactivation[27] this work will be beneficial in predicting the benefit of screening and treatment strategies in our setting.

In low incidence settings, where national TST prevalence surveys have long been abandoned and the majority of cases occur among overseas-born residents, indirect LTBI estimates based on modelled annual risks of infection in countries of birth combined with migration data are a natural approach. Our analysis incorporates both TB incidence in countries-of-birth and age, both of which have been shown to be independently associated with the prevalence of LTBI among migrants in the international literature.[6 28 29]

Limitations of our approach include that applying a constant ARTI for all residents of a particular country in a particular year obscures individual variation in risk within populations due to a range of risk factors, such as immunological status.[30]

Migrants who move from a high TB-burden setting to a low-incidence setting may do so for many different reasons and may not be representative (demographically or socioeconomically) of individuals of the same age in their country of origin,[31] which may influence their risk of having been infected. Most LTBI prevalence studies, including those in Australia,[32-34] exclusively consider refugee populations; which are often screened due to a perception of higher risk.[35] Previously published LTBI prevalence in these populations do exceed our estimates (data not shown),[32-34] however, humanitarian entrants made up only 2-3% of all migrants to Australia from 2006-2016, and we consider this unlikely to substantially impact our estimates presented here.[36] Further, we note that several international studies in migrant cohorts have resulted in similar estimates to those using our method. LTBI prevalence estimates in the entire US migrant population were provided by Shea *et al.* 2014 using results from the 1999-2000 National Health and Nutrition Examination Survey, and they reported that 18.7% of overseas-born residents had LTBI. In comparison, our method leads to an estimated prevalence of 18.0% in overseas-born Australians in 2006. A separate UK study among all migrants attending three UK medical centres (2008-2010) found 144/740 (20%) born in the Indian subcontinent (≤35 years) were IGRA positive,[6] and on equivalent subsets from the Australian migration data in 2006 (by country of birth, year of arrival and age), we estimated 20.9% to have LTBI. Overall, then, our estimates appear concordant with existing data from testing in migrant populations.

Some uncertainty must also be acknowledged due to the small amount of missing census data. Despite this, census data remains a good source of comprehensive data, and post-enumeration survey data suggested that the countries of birth of census non-respondents did not differ greatly from the census respondents,[9] meaning that although we have probably slightly underestimated the numbers with LTBI, the proportions presented should be less affected.

Our method also made the assumption that, once infected, individuals remained infected for life, and so provides information about the risk of an individual having ever been infected. No allowance was made for the possibility that individuals may clear LTBI over time since infection, for which there is evidence.[37 38] Furthermore, in some settings LTBI screening and treatment may already be systematically provided to certain migrant groups and LTBI estimates may need to account for this. This is not the case in Australia, where overseas visa applicants identified has having a CXR revealing old, inactive TB may be offered LTBI screening and treatment as part of their health follow-up,[39] however the impact of these practices on overall LTBI prevalence is likely to be small, due to the small number of migrants referred to the program.[40]

Our method combines global TB infection estimates with migration data to provide useful insights into the prevalence of latent TB in our low-incidence setting. The method could be easily repeated in any setting with reliable census data. Resulting quantitative estimates can assist in developing rational strategies for LTBI screening, which allow for opportunities to promote the long-term health of overseas-born residents and contribute towards the ultimate goal of global TB elimination.

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Katie Dale conceived the study, performed data preparation, analysis and wrote the article. Rein Houben and Pete Dodd developed the annual risk of infection estimates and assisted in data analysis. Justin Denholm and James Trauer assisted in data analysis. All authors contributed to article revisions.

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348 **Table 1 Estimated LTBI among Australian residents in 2016, with country-specific results from the ten countries of birth contributing the greatest numbers with LTBI.**

Country of birth	Percentage of Australian population (%)	Median number, in thousands, estimated to have LTBI in Australia (IQR)	Median age of resident with LTBI (years)	Median years since arrival of those estimated to have LTBI	Median percentage of all LTBI in Australia (%)	Median percentage with LTBI by age group (IQR)				
						0-14 years	15-34 years	35-64 years	≥ 65 years	All
China	2.3	113 (89-140)	53	12	11.8	1.5 (1.4-1.6)	9.1 (8.5-9.8)	29.2 (22.3-38.4)	65.6 (43.2-85.8)	21.3 (16.8-26.6)
India	2.1	115 (108-124)	36	8	12.1	2.9 (2.7-3.1)	22.9 (21.6-24.3)	31.5 (29.3-34.5)	45.9 (38.2-54.9)	26.0 (24.4-28.0)
Philippines	1.1	101 (85-117)	47	12	10.6	6.8 (6.3-7.3)	28.1 (26.5-30.0)	55.3 (45.8-66.1)	80.2 (57.4-96.0)	44.7 (37.9-51.8)
Vietnam	1.0	96 (61-125)	55	27	10.0	3.3 (3.0-3.6)	18.9 (17.0-21.4)	49.9 (29.8-70.0)	91.0 (57.8-99.9)	45.5 (29.1-59.5)
South Africa	0.7	37 (30-52)	45	9	3.8	8.2 (7.6-9.0)	16.8 (15.9-18.3)	27.4 (21.5-39.1)	25.8 (16.1-56.9)	22.9 (18.6-32.4)
Indonesia	0.3	32 (30-33)	41	13	3.3	7.9 (7.4-8.4)	34.4 (33.1-35.6)	53.1 (50.9-55.5)	67.5 (56.4-79.7)	44.6 (42.7-46.6)
Cambodia	0.2	24 (20-26)	49	25	2.6	11.5 (10.8-12.2)	50.0 (46.2-54.6)	85.6 (66.0-93.3)	100.0 (91.4-100.0)	76.0 (62.6-82.0)
South Korea	0.5	25 (23-27)	49	14	2.6	1.4 (1.3-1.6)	9.1 (8.5-9.9)	39.6 (36.0-43.2)	92.6 (84.9-97.8)	26.7 (24.5-28.5)
Pakistan	0.3	17 (15-18)	35	5	1.8	4.1 (3.8-4.4)	24.2 (23.0-25.6)	41.5 (36.0-48.5)	68.7 (54.3-79.6)	27.9 (25.4-30.9)
Myanmar	0.2	16 (13-18)	45	8	1.7	9.4 (8.5-10.2)	34.3 (32.0-36.6)	60.4 (49.4-75.7)	87.3 (61.2-98.4)	51.1 (42.6-59.1)
Other countries	19.6	413 (378-456)	56	25	39.8	0.9 (0.9-1.0)	5.4 (5.3-5.6)	10.4 (9.7-11.2)	16.8 (14.6-20.1)	10.4 (9.5-11.4)
All overseas-born	28.3	998 (943-1058)	49	15	93.2	2.1 (2.0-2.1)	11.3 (11.1-11.6)	20.1 (18.7-21.3)	22.9 (20.6-25.8)	17.1 (16.2-18.1)
Australian-born	71.7	65 (48-112)	54	-	6.8	0.1 (0.1-0.1)	0.3 (0.2-0.3)	0.6 (0.4-0.9)	0.9 (0.5-2.3)	0.4 (0.3-0.7)

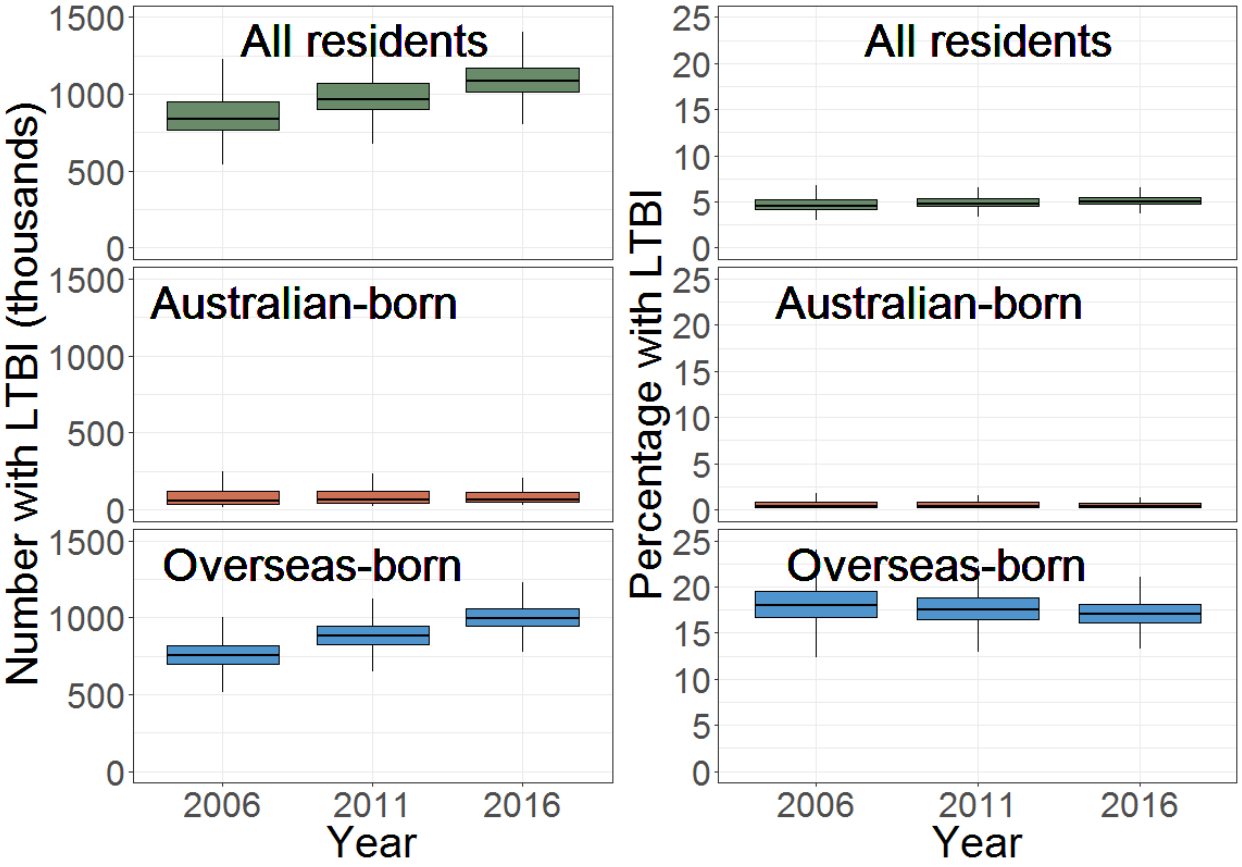


Figure 1 Number and percentage of Australians estimated to have LTBI by census year. Vertical lines represent data points that are no more than 1.5 times the interquartile range from the box.

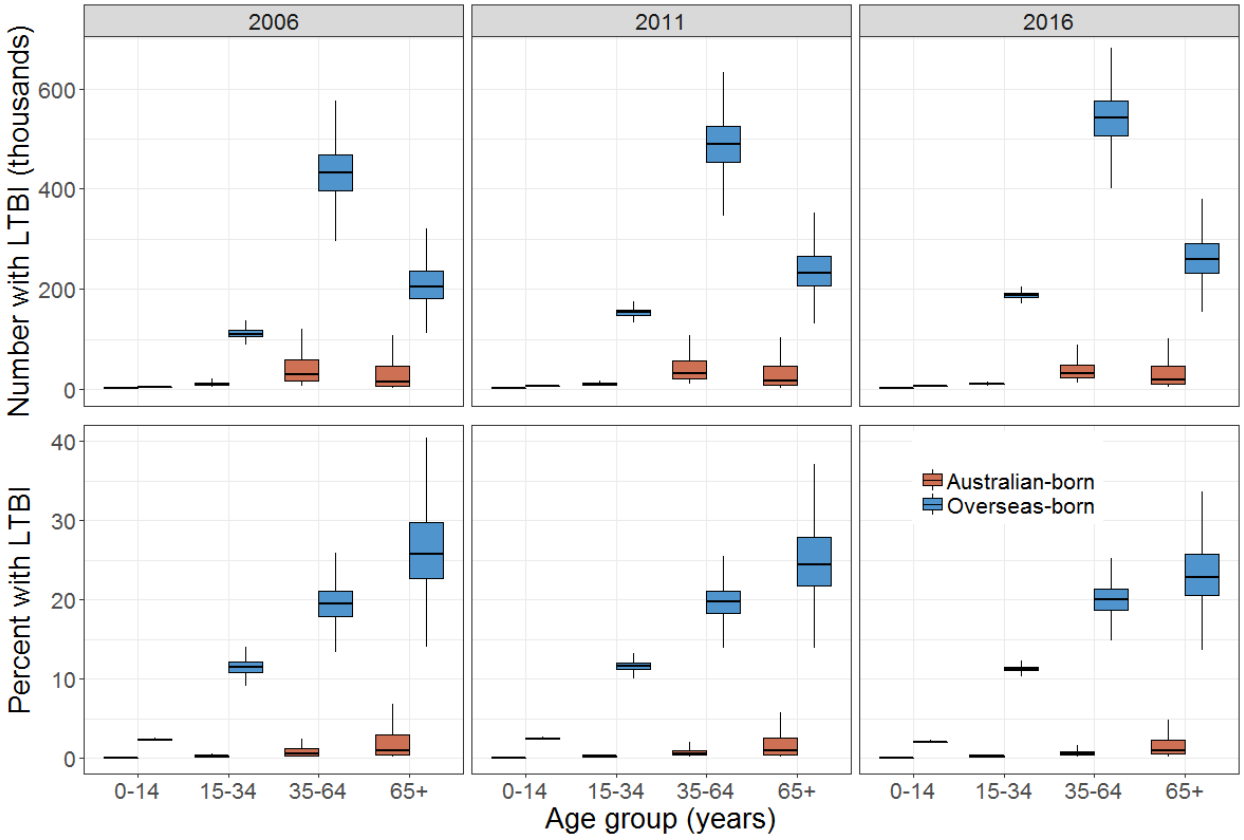


Figure 2 Estimated number and percentage estimated to have LTBI by age group and census year. Vertical lines represent data points that are no more than 1.5 times the interquartile range from the box.

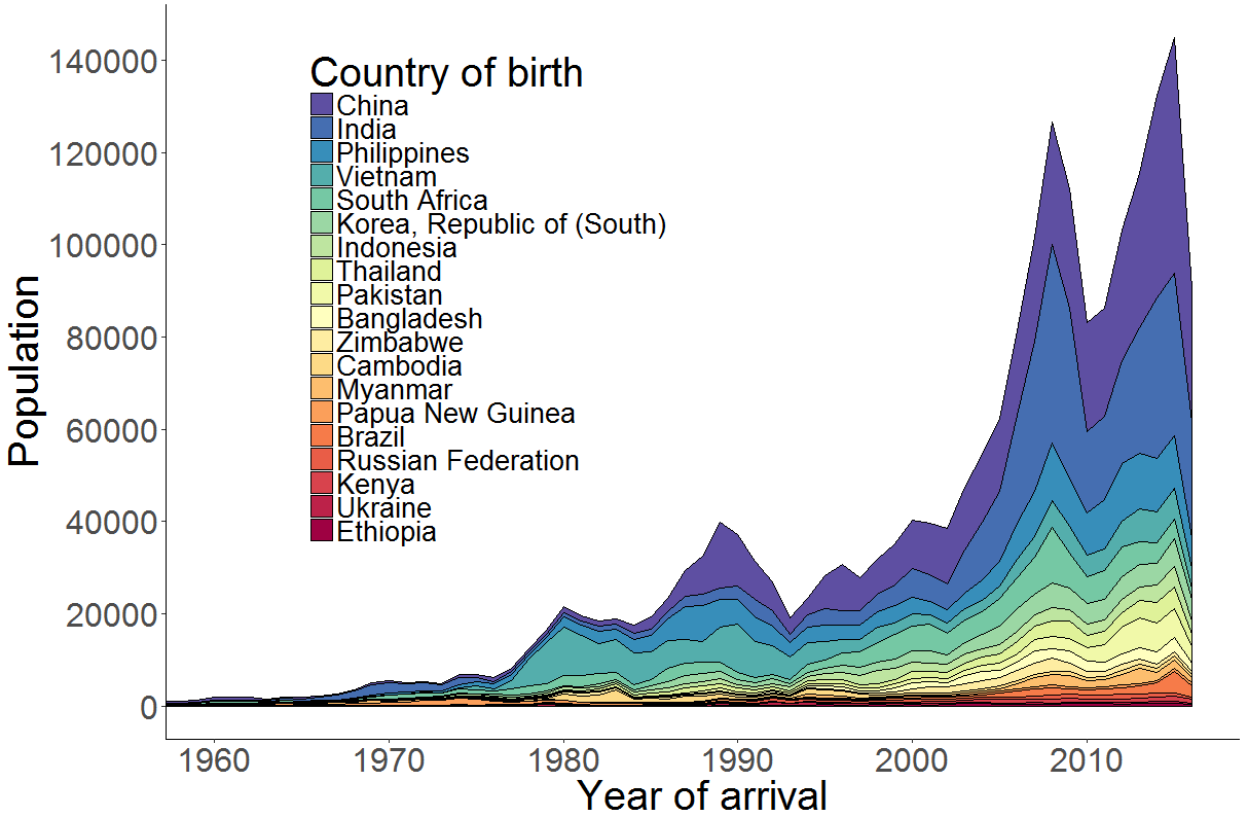


Figure 3 Number arriving by year of Australian residents in 2016 who were born in countries with a high burden of TB (as defined by the WHO 2017 Global TB Report[19]). Birth countries with fewer than 10,000 residents excluded.

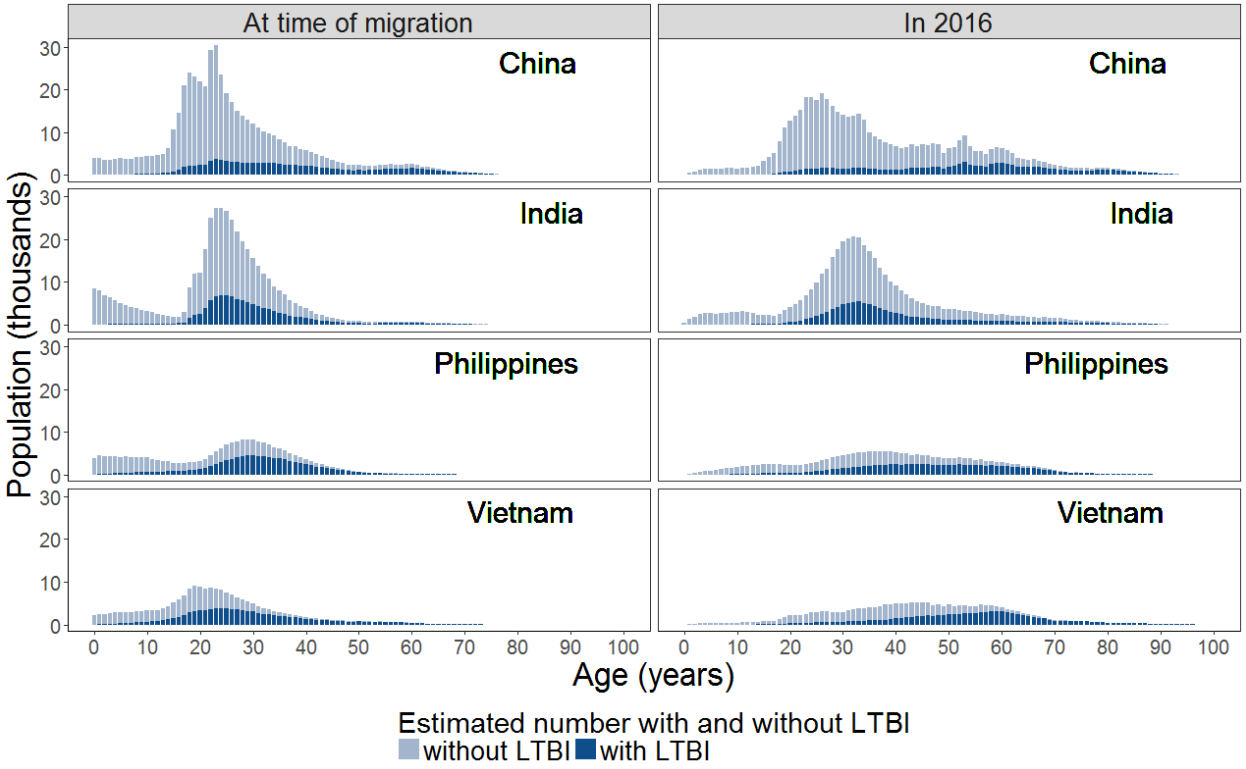


Figure 4 Estimated number of overseas-born residents in Australia for the four most common countries of birth, by age and LTBI status, at time of migration and as at the 2016 census.

Appendices

The probabilities of infection in the Australian-born (p_a) and in the overseas-born (p_o) are given by:

$$p_a = 1 - e^{-H_a}$$

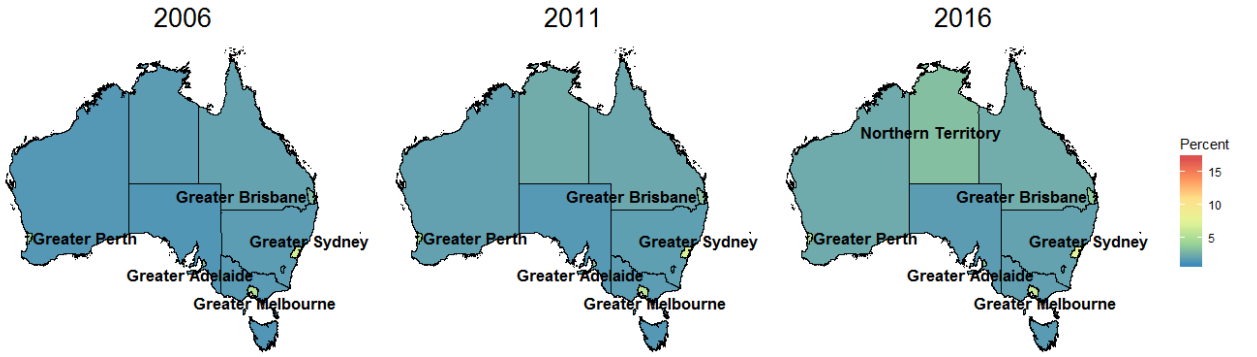
$$p_o = 1 - e^{-H_o}$$

$$H_a = {}^1/_2 FOI_{ba} + \sum_{i=b+1}^{f} FOI_{ia}$$

$$H_o = {}^1/_2 FOI_{bs} + \sum_{i=b+1}^{m-1} FOI_{is} + {}^1/_2 FOI_{ms} + {}^1/_2 FOI_{ma} + \sum_{i=m+1}^{f} FOI_{ia}$$

Where FOI indicates the force of infection that an Australian-born ($_a$) or overseas-born ($_o$) person was exposed to in a specific year and country, and *H* indicates the cumulative force of infection. The subscripts *a*, *b*, *m*, *s* and *f* refer to Australia, birth year, migration year, source country and final year of calculation respectively, and are applied to forces of infection in specific years and countries.

a)



b)

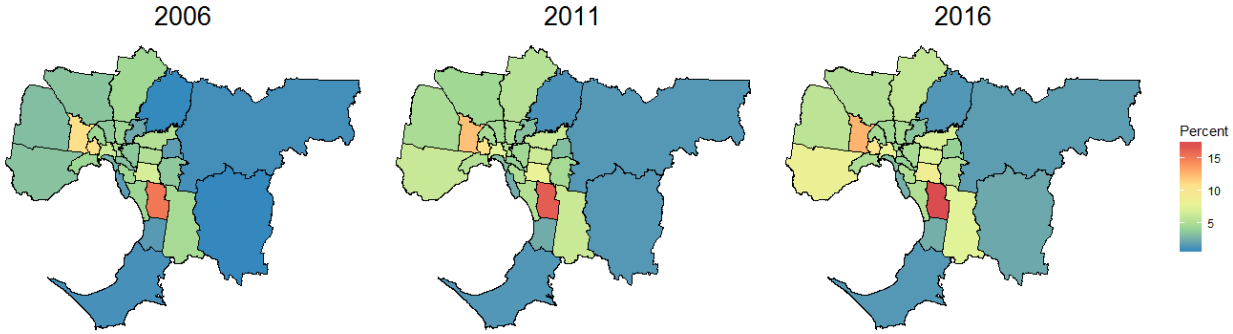


Figure S1 Estimated percentage of residents with LTBI in Australia over time by a) region of Australia and b) local government area in Greater Melbourne.