CHEST

Risk of Active Tuberculosis in the Five Years Following Infection . . . 15%?

James M. Trauer, MBBS, MPH; Nompilo Moyo, ~~MHA~~; Ee-Laine Tay, MBBS, MPhil (App Epi); Katie Dale, MPH; Romain Ragonnet, MS; Emma S. McBryde, PhD; and Justin T. Denholm, PhD, MPH

BACKGROUND: It is often stated that the lifetime risk of developing active TB after an index infection is 5% to 10%, one-half of which accrues in the 2 to 5 years following infection. The goal of this study was to determine whether such estimates are consistent with local programmatic data.

METHODS: This study included close contacts of individuals with active pulmonary TB notified in the Australian state of Victoria from January 1, 2005, to December 31, 2013, who we deemed to have been infected as a result of their exposure. Survival analysis was first performed on the assumption of complete follow-up through to the end of the study period. The analysis was then repeated with imputation of censorship for migration, death, and preventive treatment, using local mortality and migration data combined with programmatic data on the administration of preventive therapy.

RESULTS: Of 613 infected close contacts, 67 (10.9%) developed active TB during the study period. Assuming complete follow-up, the 1,650-day cumulative hazard was 11.5% (95% CI, 8.9-14.1). With imputation of censorship for death, migration, and preventive therapy, the median 1,650-day cumulative hazard over 10,000 simulations was 14.5% (95% CI, 11.1-17.9). Most risk accrued in the first 5 months after infection, and risk was greatest in the group aged < 5 years, reaching 56.0% with imputation, but it was also elevated in older children (27.6% in the group aged 5-14 years).

CONCLUSIONS: The risk of active TB following infection is several-fold higher than traditionally accepted estimates, and it is particularly high immediately following infection and in children.

CHEST 2016; 149(2):516-525

KEY WORDS: epidemiology; TB; TB prevention

ABBREVIATIONS: BCG = Bacillus Calmette-Guérin; IGRA = interferon-gamma release assay; LTBI = latent TB infection; TST = tuberculin skin test

AFFILIATIONS: From the Victorian Tuberculosis Program at the Peter Doherty Institute (Dr Trauer, Mr Moyo, and Ms Dale), Melbourne, Australia; Centre for Population Health (Dr Trauer and Mr Ragonnet), the Burnet Insitute, Melbourne, Australia; Victorian Department of Health and Human Services (Ms Tay), Melbourne, Australia; Victorian Infectious Diseases Service at the Peter Doherty Institute (Prof McBryde and Dr Denholm), Melbourne, Australia; Australian Institute of Tropical Health and Medicine (Prof McBryde), James Cook University, Australia; and the Department of Microbiology and Immunology (Dr Denholm), the University of Melbourne at the Peter Doherty Institute, Melbourne, Australia.

FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

CORRESPONDENCE TO: James M. Trauer, MBBS, MPH, Victorian TB Program at the Peter Peter Doherty Institute, 792 Elizabeth St, Melbourne 3000; e-mail: james.trauer@mh.org.au

DOI: http://dx.doi.org/10.1016/j.chest.2015.11.017

Accurate determination of the risk of future disease in subjects with latent TB infection (LTBI) is critical to understanding this disease.[1] It has been estimated that approximately one-third of the world's population is infected,[2] and close contacts are at particularly high risk.[3] Latency dynamics have implications for the individual[4] and are crucial to transmission models.[5] Much research has been conducted on the assumption that the annual risk of active disease is $< 0.3\%$,[6,7] and current information from groups such as the World Health Organization states that 5% to 10% of infected subjects will develop TB, one-half of whom will do so within 2 to 5 years.[8,9]

These estimates are based on empirical research (reviewed in more detail in the following text). However, we are unaware of modern estimates that rigorously adopt the principles of a survival analysis[10] to allow for the incomplete detection of all individuals developing active disease inherent in any surveillance system. We thus believe it is unsafe to assume that all members of a cohort of subjects who go on to develop active TB will be reliably detected through surveillance; even in settings in which case detection is very high, loss to follow-up will occur through migration, death, and preventive therapy.[11,12]

The goal of the present study was therefore to determine whether commonly accepted risk estimates are consistent with modern epidemiologic observations. Using notification data from Victoria, Australia, a subgroup of close contacts of TB cases were identified who could be determined (with a high degree of confidence) to have been infected as a result of their exposure. Survival analyses were then performed to determine risk of progression to active disease.

Materials and Methods

The full methods are described in e-Appendix 1 and are summarized as follows.

Data Source

Records for all close contacts of bacteriologically confirmed pulmonary cases prospectively identified by the Victorian Tuberculosis Program from January 1, 2005, to December 31, 2013, were extracted from an existing programmatic database obtained from surveillance records. The database contains demographic information, laboratory results, and case notes and has been previously described.[13] Analysis was performed by using Matlab Version R2015a (MathWorks). The project was approved by the Victorian Department of Health and Human Services Human Research Ethics Committee.

Definitions

The exposure date was defined as the collection date of the first specimen from the index case or estimated as 6 days prior to notification, when this information was unavailable (2.9% of contacts). LTBI was defined as results of a tuberculin skin test (TST) $\geq$ 10 mm or a positive result on the interferon-gamma release assay (IGRA), rather than the more commonly used $\geq$ 5 mm for close contacts.[14,15] LTBI conversion was defined as: a first LTBI assessment consisting of either a TST result $<$ 10 mm or a negative IGRA and an assessment performed at least 14 days later that was either a TST result $\geq$ 10 mm that had increased by $\geq$ 6 mm from baseline[16] or a positive IGRA. Low-endemic countries were defined by an incidence $<$ 15 per 100,000 per year.[17]

In Victoria, close contacts are defined as "people who have had frequent, prolonged and close contact in an enclosed environment with an infectious case such as: all people living in the same dwelling; relatives and friends who have frequent, prolonged and close contact; and work colleagues who share the same indoor work areas on a daily basis, following an individual risk assessment."[18]

Survival Analyses

Close contacts of bacteriologically confirmed index pulmonary cases were included in the analysis if they either demonstrated conversion or were born in a low-endemic country and had a positive LTBI assessment recorded during contact investigations. This definition was intended to be highly specific, ensuring with a high degree of confidence that the study cohort consisted only of individuals determined to be infected. However, several alternative definitions are also considered (Table 1).

Survival analyses were first performed on raw data with universal censorship at December 31, 2013. Survival analyses were then performed with imputation of censorship due to death, migration, or treatment-related protection from reactivation. Imputed analysis was performed 10,000 times, with the individual-level probability of censorship due to each cause drawn from plausible ranges and then randomly imputed at the individual level (Fig 1).

Censorship Imputation

Case notes of all 776 infected contacts included in any of the alternative analyses presented were reviewed to determine whether and when preventive therapy was commenced. In the main analysis cohort of 613, a total of 44 contacts infected by isoniazid-resistant strains were presumed not to have received effective preventive therapy, as were 121 contacts for whom case records suggested they had not completed treatment and the 67 contacts who developed active TB. Of the remaining 381 contacts, 65 were known to have completed a full course of preventive treatment; 134 started treatment, but their completion status was uncertain; and the treatment status of 182 contacts could not be determined. Treatment efficacy was estimated at 87.5% (ie, approximately 85%-90%)[11,19,20] and compliance at 85%.[21] Therefore, the 65 contacts known to have completed treatment were conferred a 87.5% chance of censorship due to preventive therapy, whereas the 134 contacts with uncertain completion status were conferred a 74.4% chance of censorship ($87.5\% \times 85\%$). The 182 contacts for whom information was unavailable were conferred a probability of treatment by using a β-cumulative distribution function with parameters 3.81 and 2 (e-Fig 1), multiplied by 74.4% to incorporate compliance and efficacy. Of the 199 contacts known to have commenced treatment, the start date was known in 169 (84.9%). For the remainder and for the 182 contacts with no data, start dates were estimated at approximately 100 days from infection.

TABLE 1] Results According to Age Group Considering Alternative Definitions of Infected Contact: Raw and With Imputation

Definition of Infection	Cases	Contacts	All Ages		Aged < 5 Years		Aged 5 to 14 Years		Aged ≥ 15 Years	
			Raw Data	With Imputation	Raw Data	With Imputation	Raw Data	With Imputation	Raw Data	With Imputation
Conversion or TST ≥ 5 mm,[a] low endemic[b]	69	776	9.3 (7.2-11.4) 1,650 days	11.7 (9.0-14.5)	30.8 (21.5-40.2) 144 days	47.8 (34.1-61.4)	17.6 (11.7-23.4) 906 days	23.0 (15.3-30.7)	2.6 (1.0-4.3) 1,650 days	3.6 (1.4-5.9)
Conversion or TST ≥ 10 mm,[a] low endemic	67	613	11.5 (8.9-14.1) 1,650 days	14.5[c] (11.1-17.9)	36.2 (25.7-46.8) 144 days	56.0 (41.1-70.9)	20.7 (13.7-27.7) 906 days	27.6 (18.3-37.0)	3.4 (1.3-5.5) 1,650 days	4.7 (1.8-7.7)
Conversion	21	258	8.6 (5.1-12.2) 970 days	11.8 (6.9-16.7)	24.2 (7.3-41.1) 144 days	47.1 (16.8-77.5)	17.2 (7.0-27.4) 144 days	25.5 (10.8-40.3)	3.9 (0.8-6.9) 970 days	5.4 (1.1-9.7)
TST ≥ 5 mm,[a] low endemic	58	604	10.0 (7.5-12.4) 1,650 days	12.3 (9.2-15.5)	31.8 (22.0-41.5) 144 days	48.6 (34.7-62.5)	17.5 (11.3-23.8) 906 days	22.3 (14.2-30.3)	1.8 (0.2-3.5) 1,650 days	2.4 (0.1-4.8)
TST ≥ 10 mm,[a] low endemic	56	441	13.2 (9.9-16.5) 1,650 days	16.5 (12.3-20.7)	37.8 (26.7-48.9) 144 days	57.4 (42.3-72.5)	21.3 (13.5-29.0) 906 days	27.7 (17.6-37.8)	2.7 (0.2-5.1) 1,650 days	3.6 (0.1-7.1)
Conversion, BCG naive or TST ≥ 5 mm,[a] low endemic, BCG naive	47	238	20.0 (14.9-25.1) 906 days	25.5 (18.9-32.0)	47.2 (34.2-60.2) 144 days	68.1 (51.7-84.5)	23.5 (14.2-32.8) 906 days	30.8 (18.6-43.0)	1.0 (0.0-3.0) 47 days	1.1 (0.0-3.4)

(Continued)

TABLE 1] *(Continued)*

Definition of Infection	Cases	Contacts	All Ages		Aged < 5 Years		Aged 5 to 14 Years		Aged ≥ 15 Years	
			Raw Data	With Imputation	Raw Data	With Imputation	Raw Data	With Imputation	Raw Data	With Imputation
Conversion, BCG naive or TST ≥ 10 mm,[a] low endemic, BCG naive	46	203	23.0 (17.1-28.8) 906 days	29.6 (22.1-37.2)	50.8 (37.2-64.3) 144 days	73.0 (56.8-89.3)	26.9 (16.2-37.6) 906 days	36.0 (21.9-50.1)	1.2 (0.0-3.7) 47 days	1.4 (0.0-4.1)
Conversion, BCG naive	10	56	18.6 (8.2-29.0) 144 days	23.1 (10.3-35.9)	44.4 (15.2-73.7) 144 days	66.7 (29.9-100.0)	30.4 (8.1-52.8) 142 days	39.2 (11.8-66.6)	0	0
TST ≥ 5 mm,[a] low endemic, BCG naive	45	223	20.4 (15.1-25.7) 906 days	26.2 (19.3-33.0)	46.3 (33.2-59.4) 144 days	67.6 (51.0-84.2)	23.0 (13.6-32.4) 906 days	29.7 (17.6-41.8)	1.2 (0.0-3.4) 47 days	1.3 (0.0-3.9)
TST ≥ 10 mm,[a] low endemic, BCG naive	44	188	23.7 (17.6-29.9) 906 days	30.9 (22.9-38.8)	49.8 (36.2-63.5) 144 days	72.7 (56.1-89.2)	26.4 (15.6-37.3) 906 days	34.8 (20.7-48.9)	1.4 (0.0-4.3) 47 days	1.6 (0.0-4.8)

The time period for all analyses With Imputation is equal to that for the Raw Data. BCG = Bacillus Calmette-Guérin; IGRA = interferon-gamma release assay; TST = tuberculin skin test.
[a]Or positive result on IGRA (although diagnosis is primarily TST-based).
[b]Selected a priori as the primary analysis.
[c]See e-Figure 2.

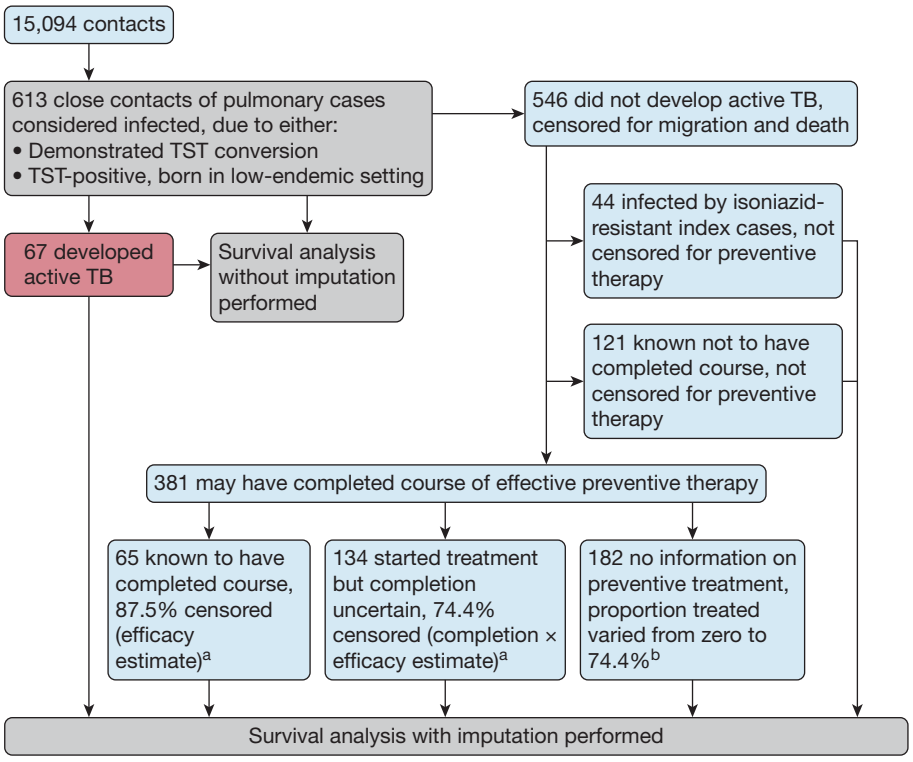


Figure 1 – *Flowchart of approach to analysis.* [a]*Actual treatment start dates used where available (83%) and imputed at an average 100 days when unknown.* [b]*Simulated proportion commenced on treatment varied from zero to one, which was then multiplied by 74.4% to incorporate compliance and efficacy, with average date of censorship 100 days from infection date. TST = tuberculin skin test.*

Total interstate and overseas migration were estimated at 0.6% ± 0.1% per year by using data from the Australian Bureau of Statistics.[22] Age, sex, and calendar year-specific mortality rates were also obtained from the Australian Bureau of Statistics[23] and applied individually to each contact, with a variation of ± 20%.

Results

Of the 15,094 contacts identified over the study period, 613 met the study criteria for infection at the time of exposure, and the characteristics of these cases are presented in Table 2. Results differed markedly according to age, with 29 of 81 (35.8%) aged < 5 years, 27 of 136 (17.4%) aged 5 to 14 years, and 11 of 396 (2.8%) aged ≥ 15 years developing TB. Of the 67 cases of active TB, 64 met the full case definition,[18] and three were classified as presumptive cases; all cases were treated with a full course of therapy for active disease.

Survival Analysis Without Imputation

The left-hand panels of Figure 2 and the alternate columns of Table 1 and e-Table 1 present the results from survival analyses without imputation. Most risk (10.2%) accrued over the first 227 days and the 1-, 2-, 3-, and 4-year risks of active TB were 10.2%, 10.4%, 10.9%, and 11.1%, respectively. The pattern of reactivation differed markedly according to age group, with the risk highest in the group aged < 5 years, intermediate in the group aged 5 to 14 years, and lowest in the group aged ≥ 15 years. In the younger two age groups, virtually all risk accrued within 5 months (36.2% over 144 days for those aged < 5 years; 19.7% over 145 days for those aged 5-14 years), with negligible risk thereafter. By contrast, in those aged ≥ 15 years, risk was more evenly distributed, with approximately one-half the total risk accruing within the first 227 days. The abrupt transition from high to low risk is seen more clearly if a less specific definition for infection is used (e-Figure 3).

Survival Analysis With Imputation

The right-hand panels of Figure 2 and the alternate columns of Table 1 display the results from survival analyses with imputation. The median cumulative hazard over 10,000 simulations was 14.5% with 1,650 days of follow-up; 12.5% accrued in the first 227 days and the 1-, 2-, 3-, and 4-year risks of active TB were 12.5%, 12.8%, 13.5%, and 14.0%, respectively. Estimated risks for the groups aged < 5 years, 5 to 14 years, and ≥ 15 years were 56.0%, 27.6%, and 4.7%.

Alternative Analyses

Table 1 also presents results from analyses by using various alternative definitions of infection. Depending

TABLE 2] Characteristics of Infected Contacts Included in Analysis (N = 613)

Characteristic	Value
Female sex	297 (48.5)
Age, median (IQR), y	23.7 (9.0-43.4)
Age, y	
< 5	81 (13.2)
5-14	136 (22.2)
≥ 15	396 (64.6)
Infected by smear-positive index case	393 (64.1)
Infected by isoniazid-resistant index case	47 (7.7)
BCG vaccinated	353 (57.6)
BCG status uncertain	57 (9.3)
BCG naive	203 (33.1)
Known immunocompromise[a]	0
Conversions	258 (42.1)
Conversion on TST results	253 (98.1)
Conversion on IGRA results	32 (12.4)
Positive result from low-endemic setting	441 (71.9)
Positive result from low-endemic setting on TST results	423 (95.9)
Positive result from low-endemic setting on IGRA results	46 (10.4)

Data are presented as no. (%) unless otherwise indicated. Conversions and positive results from low-endemic settings do not sum to 613 because 86 contacts were included in both categories. Similarly, diagnoses made by using TST and IGRA results do not sum to the total diagnoses because contacts may have met criteria on both investigations. Diagnoses made on TST or IGRA are presented as percentages of conversions or positive results from low-endemic settings. IQR = interquartile range. See Table 1 legend for expansion of other abbreviations.

[a]HIV status collected from 2009 onward; significant immunosuppressive medication field collected throughout; no mention of immunocompromise in case notes.

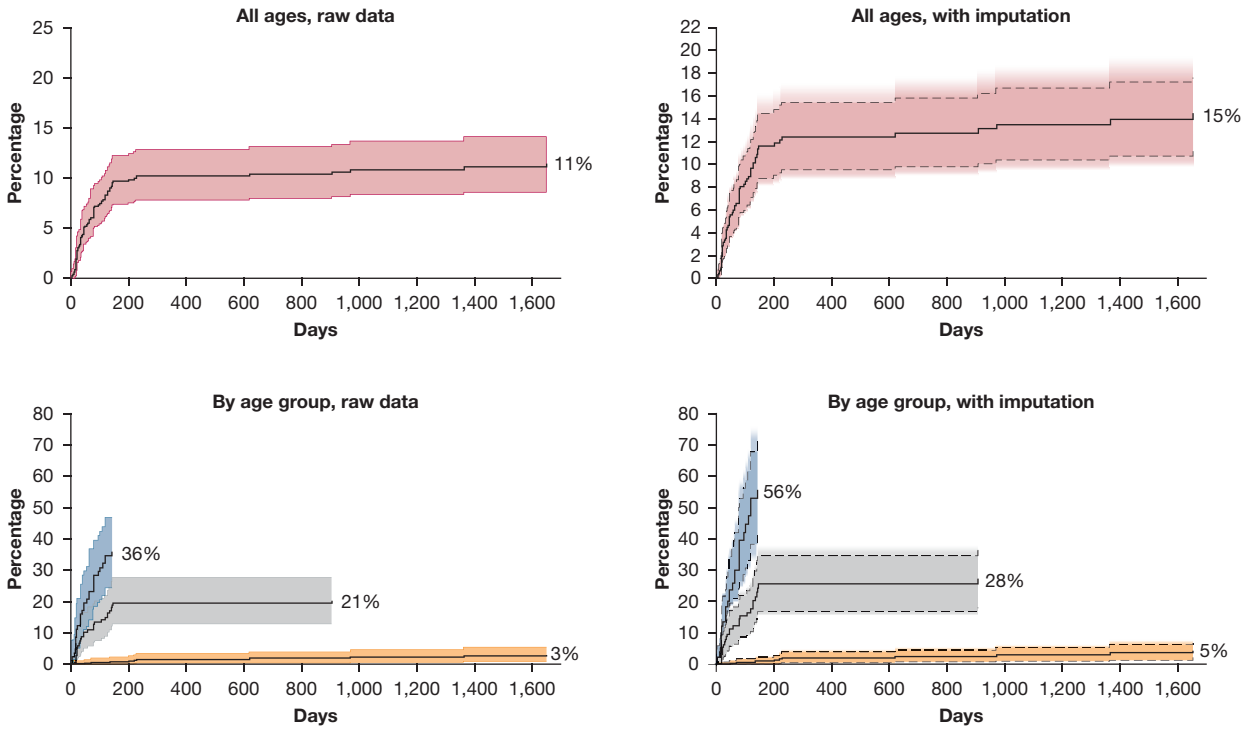
on the definition used, the point estimate of the risk (with imputation of censorship) of TB varied from approximately 12% to > 30%. Analyses included varying the TST cutoff used and absence of a history of Bacillus Calmette-Guérin (BCG) vaccination. However, when analysis was restricted to BCG-naive contacts only, the size of the cohort diminished to the point that precise estimates of risk could not be derived.

Discussion

We estimated the $4^1/_2$-year risk of active TB following an index infection at 14.5% by using a realistic reconstruction of a true survival analysis of contacts who could confidently determine that they had been infected at the time of their exposure. Moreover, even with less specific definitions for infection at time of exposure, our point estimates of risk remained > 11%. These values are considerably higher than the widely accepted estimates of 5% to 10% lifetime risk, with one-half occurring within 2 to 5 years, which would imply a 5-year risk of < 5%. Moreover, even our raw estimate of 11.5% is more than double this mark, and the discrepancy is thus not solely attributable to our imputation methods. Although rates of disease were more consistent with previous estimates in adults, risk was very high in the younger age groups, particularly the group aged < 5 years, reaching more than one in two. Although young children are known to be a high-risk group,[24] our findings illustrate how extreme this risk is and demonstrate that older children are also at very high risk, contradicting the proposition that age has little impact after the age of 5 years.[1] In addition, the clear differences in timing of progression to active disease by age group imply fundamental biological differences between children and adults, as late reactivation disease was virtually absent from the younger age groups.

It is important to emphasize that our analysis applies only to individuals meeting our intentionally specific definition of infection and should not be applied to other groups. Close contacts with LTBI are known to be at particularly high risk, and the risk is moderately increased if a TST conversion is observed.[25] In general, the specificity of the diagnosis of infection increases as the TST threshold increases,[26] and we selected a TST cutoff of 10 mm, rather than the more commonly used 5 mm. However, it should also be noted that this higher risk of active disease is not due to a greater risk of progression after infection but to a more specific definition of infection. Nontuberculous mycobacterial infection is unlikely to significantly confound our results in this low prevalence setting.[27] However, BCG-related false-positive results may have led to our primary analysis underestimating the true risk, as BCG-naive children seemed at higher risk than vaccinated children, which is consistent with other research.[28]

Our estimates without imputation are markedly similar to data from infected contacts in Amsterdam.[29] In that study, investigators found an overall 5-year hazard of 9.5% and age-specific estimates of 33.3%, 19.1%, and 6.7% for those aged < 5 years, 5 to 14 years, and ≥ 15 years, respectively. In addition, the change in hazard estimates according to age group over time seemed similar, validating the findings of both studies. An important difference between that analysis and the one presented here is that the Dutch study used a



print & web 4C/FPO

Figure 2 – *Survival analysis time of active TB onset in infected contacts; infection was defined as demonstrated conversion or TST result ≥ 10 mm in a person from a low-endemic setting. Upper panels provide data on all contacts; lower panels provide data on contacts stratified according to age group. Blue, aged < 5 years; gray, aged 5 to 14 years; yellow, aged ≥ 15 years. Left panels include the raw data without imputation (ie, assuming complete follow-up with censorship at December 31, 2013). Black line indicates the point estimate; shaded areas indicate 95% CIs. Right ~~panel illustrates~~, the same analysis but with imputation of censorship due to preventive therapy, migration, and death. Black line indicates point estimates for 50th centile of imputation runs; dashed lines and central shaded area indicate upper and lower confidence limits for 50th centile of imputation runs; and the lightly shaded areas indicate the upper and lower confidence limits for outer 51st to 100th centiles of imputation runs. See Figure 1 legend for expansion of other abbreviation.*

considerably less specific definition, potentially implying even higher rates of reactivation.

Other recent estimates include a study of the relative accuracy of TST and IGRA performed in close contacts in Hamburg, Germany.[30] Although only 10 of 207 (4.8%) TST-positive patients progressed to active TB over 3 years, the group may also have included a significant number of individuals infected at previous exposures. Moreover, 19 of 147 (12.9%) IGRA-positive close contacts progressed to active disease during the study period, demonstrating the ability of a more specific diagnostic test to identify a higher risk cohort. Another Dutch study found that 7 of 184 (3.8%) close contacts of smear-positive index cases aged ≥ 16 years with a TST result ≥ 10 mm progressed to active TB over approximately 2 years, which is also consistent with our estimates.[31]

Earlier empirical estimates of reactivation risk include those from the control arm of the United States Public Health Service trials of isoniazid. In these trials, 147 of 4,992 (2.9%) close contacts of index cases with positive TST results developed active TB over 10 years. However, these results likely included some individuals with positive results on TSTs from previous exposure and these results date from the 1950s, at which time TB diagnostics and surveillance systems are likely to have been considerably less sensitive.[32] Similar issues may have affected the estimates of disease rates among children from the general community with a TST result ≥ 6 mm enrolled in a controlled trial of BCG vaccination in Puerto Rico during a similar era.[33] In that study, 1,400 of 82,269 (1.7%) children developed active disease. Other studies from the same era have found higher rates of active TB in contacts, including a trial of home versus hospital antituberculous chemotherapy from south India, in which 62 of 528 (11.7%) contacts developed active TB over 5 years.[34] Similarly, in the Phillipines, 18 of 129 (14.0%) TST-positive close contacts of patients with cavitatory disease who received placebo developed chest radiograph abnormalities within 2 years.[32]

Seminal modeling studies from the United Kingdom and the Netherlands have produced higher estimates for rates of primary progression to active TB,[35] including estimates

of 12%[36] and even 5.5% per year for 5 years.[37] These studies fit dynamic TB transmission models to 20th century notification data from these countries. Given the inevitability of losing some individuals to follow-up when studying cohorts of TB contacts, these studies provide an alternative approach to estimating risk over time. Although such methods also have limitations, the discrepancy from traditional estimates of risk is notable.

Sensitivity analysis (e-Appendix 1, e-Fig 4) indicated that our estimate of 14.5% of infected contacts progressing to active TB within 5 years could underestimate or overestimate the true value by approximately 3%. Several alternative analyses implied even higher risk if more specific definitions of infection were adopted, whereas most of the assumptions (Table 3) inherent in the study analysis would be expected to have little impact on our estimates. The assumption that subsequent cases of active TB occurring in contacts in Victoria are universally the result of the identified index case is an important consideration because re-exposure and subsequent TB in contacts could lead to overestimation of the hazard of TB following the index infection. However, because the rate of active TB in Victoria was 6.6 per 100,000 per year in 2012 to 2013, the rate of TB transmission in our population can be considered negligible.[38] In support of this proposition a review of the risk factors of the 67 active cases included in this study indicated that only seven had additional risk factors to being a close contact. Moreover, the absence of any cases in the group aged < 5 years after the first few months of exposure implied no further transmission to this highest risk group.

TABLE 3] Assumptions Influencing Imputed Estimates of Cumulative Hazard

Assumptions biasing toward an underestimate of true risk
Complete capture of active TB cases through notification systems in Victoria, Australia
Complete linkage of all active cases to the index case from which they were acquired
Those at higher risk of progression are not clinically targeted for preventive treatment
No isoniazid-resistant contacts were enrolled in the studies used to estimate efficacy of preventive treatment
Assumptions biasing estimate in either direction but more likely to result in underestimation
Contacts do not have different/higher mortality rates compared with the general Victorian population[a]
Contacts do not have different/higher migration rates compared with the general Victorian population[a]
Assumptions biasing estimate in either direction
Proportion of contacts effectively commenced on preventive therapy[a]
Time from identification of contact to commencement of preventive therapy[a]
Proportion of patients commencing preventive therapy who complete treatment[a]
Efficacy of preventive therapy
Assumption biasing estimate to an overestimate of true risk
All subsequent cases of TB in contacts are due to the index exposure identified

[a]Explored in sensitivity analyses.

The parameter with the greatest potential to influence our conclusions was our assumption regarding the effectiveness of preventive therapy. We applied a conservative efficacy estimate of 85% to 90% to contacts infected by isoniazid-sensitive cases only. This estimate is based on the per-protocol estimate of a 52-week regimen from the largest randomized, placebo-controlled trial in isoniazid preventive therapy, which also reported an efficacy of 69% for the 24-week regimen arm,[19] and is consistent with other such trials.[39] Interpolation from these data suggest that 9 to 10 months of treatment was the optimal duration[20]; although efficacy of the 9-month regimen has been compared with other regimens,[40] its efficacy has not been compared with placebo. Despite this finding, 9-month regimens of isoniazid are considered highly effective across a range of populations,[41] including children.[42] A systematic review and meta-analysis of the efficacy of this treatment in children found results similar to those we applied to adults, except that efficacy was attenuated in those aged < 4 months,[43] an age group that constituted 0.6% of our study population. Similarly, unrecognized immunocompromise should have little impact on our estimates: none of the 67 reactivation cases were known to have been HIV positive (although data were only available from 2009 onward), the Victorian HIV population prevalence is approximately 0.1%, and no contacts were reportedly receiving immunosuppressive medication.[44]

Conclusions

The 5-year risk of active TB after infection was estimated at 11% to 18%, and this value is more likely to be an underestimate than an overestimate. Although this value is approximately twofold to sevenfold the traditionally accepted rate, our estimates are consistent with much of the previous research. Because the risk of developing active TB is likely to be higher in developing countries,[3] as well as in populations with a high prevalence of

comorbidities, even higher levels of risk may be present in such settings. Our estimates allow more accurate assessment of the effectiveness and cost-effectiveness of contact tracing programs, highlighting the potential impact from preventive therapy and the importance of initiating such treatment soon after infection.

Acknowledgments

Author contributions: J. M. T. affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. J. M. T. conceived the study, developed the analysis approach, performed the analysis, and drafted the manuscript. N. M. and E.-L. T. compiled the broader database from which the subjects were identified. K. D. assessed records for preventive therapy administration. R. R. and E. S. B. advised on the approach to analysis. J. T. D. supervised the study.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: J. M. T. is a National Health and Medical Research Council scholarship recipient for doctoral studies in TB. E. S. M. is a National Health and Medical Research Council Career Development Fellowship recipient. None declared (N. M. E.-L. T., K. D., R. R., J. T. D.).

Additional information: The e-Appendix, e-Figures, and e-Table can be found in the Supplemental Materials section of the online article.

References

1. Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent Mycobacterium tuberculosis infection. *N Engl J Med*. 2015;372(22):2127-2135.
2. Corbett EL, Watt CJ, Walker N, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med*. 2003;163(9):1009-1021.
3. Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Respir J*. 2013;41(1):140-156.
4. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement. *Am J Respir Crit Care Med*. 2000;161(4 pt 2):S221-S247.
5. Dowdy DW, Dye C, Cohen T. Data needs for evidence-based decisions: a tuberculosis modeler's 'wish list.' *Int J Tuberc Lung Dis*. 2013;17(7):866-877.
6. Jasmer RM, Snyder DC, Saukkonen JJ, et al. Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a cost-effectiveness analysis based on a multicenter clinical trial. *Clin Infect Dis*. 2004;38(3):363-369.
7. Salpeter SR, Sanders GD, Salpeter EE, Owens DK. Monitored isoniazid prophylaxis for low-risk tuberculin reactors older than 35 years of age: a risk-benefit and cost-effectiveness analysis. *Ann Intern Med*. 1997;127(12):1051-1061.
8. Centers for Disease Control and Prevention. Tuberculosis (TB) fact sheets: the difference between latent TB infection and TB diseases. http://www.cdc.gov/tb/publications/factsheets/general/ltbiandactivetb.htm. Accessed May 29, 2015.
9. World Health Organization. Latent tuberculosis infection (LTBI). http://www.who.int/tb/challenges/ltbi/en/. Accessed May 29, 2015.
10. von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335(7624):806-808.
11. Smieja MJ, Marchetti CA, Cook DJ, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. *Cochrane Database Syst Rev*. 2000;(2):CD001363.
12. Comstock GW, Baum C, Snider DE Jr. Isoniazid prophylaxis among Alaskan Eskimos: a final report of the Bethel isoniazid studies. *Am Rev Respir Dis*. 1979;119(5):827-830.
13. Moyo N, Tay EL, Denholm JT. Evaluation of tuberculin skin testing in tuberculosis contacts in Victoria, Australia 2005-2013. *Public Health Action*. 2015;5(3):188-193.
14. Centers for Disease Control and Prevention. TB elimination, tuberculin skin testing. http://www.cdc.gov/tb/publications/factsheets/testing/skintesting.pdf. Accessed July 2, 2015.
15. Reichler MR, Reves R, Bur S, et al. Evaluation of investigations conducted to detect and prevent transmission of tuberculosis. *JAMA*. 2002;287(8):991-995.
16. Menzies D. Interpretation of repeated tuberculin tests. Boosting, conversion, and reversion. *Am J Respir Crit Care Med*. 1999;159(1):15-21.
17. The World Bank. Incidence of tuberculosis (per 100,000 people). http://data.worldbank.org/indicator/SH.TBS.INCD/countries. Accessed May 15, 2015.
18. Australian Government, Department of Health. Tuberculosis case definition. http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_tb.htm. Accessed July 2, 2015.
19. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis. *Bull World Health Organization*. 1982;60(4):555-564.
20. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int J Tuberc Lung Dis*. 1999;3(10):847-850.
21. Denholm JT, McBryde ES, Eisen DP, Penington JS, Chen C, Street AC. Adverse effects of isoniazid preventative therapy for latent tuberculosis infection: a prospective cohort study. *Drug Healthc Patient Saf*. 2014;6:145-149.
22. Australian Bureau of Statistics. 3101.0 Australian demographic statistics. Interstate departures, states and territories (persons). http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3101.0Sep%202014?OpenDocument. Accessed May 28, 2015.
23. Australian Bureau of Statistics. 3302.0, Deaths, Australia, 2013. Death rates, states and territories, 2003 to 2013. http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3302.02013?OpenDocument. Accessed May 28, 2015.
24. Beyers N, Gie RP, Schaaf HS, et al. A prospective evaluation of children under the age of 5 years living in the same household as adults with recently diagnosed pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 1997;1(1):38-43.
25. Horsburgh CR Jr. Priorities for the treatment of latent tuberculosis infection in the United States. *N Engl J Med*. 2004;350(20):2060-2067.
26. Berkel GM, Cobelens FG, de Vries G, Draayer-Jansen IW, Borgdorff MW. Tuberculin skin test: estimation of positive and negative predictive values from routine data. *Int J Tuberc Lung Dis*. 2005;9(3):310-316.
27. Farhat M, Greenaway C, Pai M, Menzies D. False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria? *Int J Tuberc Lung Dis*. 2006;10(11):1192-1204.
28. Moran-Mendoza O, Marion SA, Elwood K, Patrick D, FitzGerald JM. Risk factors for developing tuberculosis: a 12-year follow-up of contacts of tuberculosis cases. *Int J Tuberc Lung Dis*. 2010;14(9):1112-1119.
29. Sloot R, Schim van der Loeff MF, Kouw PM, Borgdorff MW. Risk of tuberculosis after recent exposure. A 10-year follow-up study of contacts in Amsterdam. *Am J Respir Crit Care Med*. 2014;190(9):1044-1052.

30. Diel R, Loddenkemper R, Niemann S, Meywald-Walter K, Nienhaus A. Negative and positive predictive value of a whole-blood interferon-gamma release assay for developing active tuberculosis: an update. *Am J Respir Crit Care Med*. 2011;183(1):88-95.

31. Kik SV, Franken WP, Mensen M, et al. Predictive value for progression to tuberculosis by IGRA and TST in immigrant contacts. *Eur Respir J*. 2010;35(6):1346-1353.

32. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. *Bibl Tuberc*. 1970;26:28-106.

33. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol*. 1974;99(2):131-138.

34. Kamat SR, Dawson JJ, Devadatta S, et al. A controlled study of the influence of segregation of tuberculous patients for one year on the attack rate of tuberculosis in a 5-year period in close family contacts in South India. *Bull World Health Organization*. 1966;34(4):517-532.

35. Vynnycky E, Fine PE. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. *Epidemiol Infect*. 1997;119(2):183-201.

36. Vynnycky E, Fine PE. Lifetime risks, incubation period, and serial interval of tuberculosis. *Am J Epidemiol*. 2000;152(3):247-263.

37. Sutherland I, Svandova E, Radhakrishna S. The development of clinical tuberculosis following infection with tubercle bacilli. 1. A theoretical model for the development of clinical tuberculosis following infection, linking from data on the risk of tuberculous infection and the incidence of clinical tuberculosis in the Netherlands. *Tubercle*. 1982;63(4):255-268.

38. Toms C, Stapledon R, Waring J, Douglas P. National Tuberculosis Advisory Committee for the Communicable Diseases Network of Australia. Tuberculosis notifications in Australia, 2012 and 2013. *Communicable Diseases Intelligence Quarterly Report*. 2015. http://www.health.gov.au/internet/main/publishing.nsf/content/cda-pubs-annlrpt-tbannrep.htm. Accessed December 30, 2105.

39. Egsmose T, Ang'awa JO, Poti SJ. The use of isoniazid among household contacts of open cases of pulmonary tuberculosis. *Bull World Health Organiz*. 1965;33(3):419-433.

40. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011;365(23):2155-2166.

41. Denholm JT, McBryde ES. The use of anti-tuberculosis therapy for latent TB infection. *Infect Drug Resist*. 2010;3:63-72.

42. Mount FW, Ferebee SH. Preventive effects of isoniazid in the treatment of primary tuberculosis in children. *N Engl J Med*. 1961;265:713-721.

43. Ayieko J, Abuogi L, Simchowitz B, Bukusi EA, Smith AH, Reingold A. Efficacy of isoniazid prophylactic therapy in prevention of tuberculosis in children: a meta-analysis. *BMC Infect Dis*. 2014;14:91.

44. The Kirby Institute. *HIV, Viral Hepatitis and Sexually Transmissible Infections in Australia Annual Surveillance Report 2013*. Sydney, Australia: The Kirby Institute, the University of New South Wales; 2013.