Are we underestimating the annual risk of infection with *Mycobacterium tuberculosis* in high-burden settings?

David W Dowdy, Marcel A Behr

The annual risk of infection with *Mycobacterium tuberculosis* determines a population's exposure level and thus the fraction of incident tuberculosis resulting from recent infection (often considered as having occurred within the past 2 years). Contemporary annual risk of infection estimates centre around 1% in most high-burden countries. We present three arguments why these estimates—primarily derived from cross-sectional tuberculin surveys in young school children (aged 5–12 years)—might underrepresent the true annual risk of infection. First, young children are expected to have lower risk of infection than older adolescents and adults (ie, those aged 15 years and older). Second, exposure might not lead to a positive test result in some individuals. Third, cross-sectional surveys might overlook transient immune responses. Accounting for these biases, the true annual risk of infection among adults in high-burden settings is probably closer to 5–10%. Consequently, most tuberculosis in those settings should reflect infection within the past 2 years rather than remote infection occurring many years ago. Under this reframing, major reductions in tuberculosis incidence could be achievable by focusing on the minority of people who have been recently infected.

Lancet Infect Dis 2022; 22: e271–78

Published Online May 5, 2022 https://doi.org/10.1016/S1473-3099(22)00153-0

Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (D W Dowdy PhD); **McGill International Tuberculosis Centre and Department of Medicine, McGill University, Montreal, QC, Canada** (Prof M A Behr MD)

Correspondence to: Dr David W Dowdy, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA **ddowdy1@jhmi.edu**

Background

An estimated 10 million people develop tuberculosis every year; 85–90% of these people live in one of 30 high-burden countries.[1] To develop an appropriate response to tuberculosis epidemics in high-burden settings, a key question is: what fraction of incident tuberculosis represents early progression from recent infection (ie, often considered as having occurred within the past 2 years), versus late progression from infection many years ago? If most cases represent recent transmission, then interventions to interrupt transmission (eg, case-finding and contact investigation) should be prioritised—and rapid progress might be achievable. If most cases represent late progression, then meaningful progress in reducing tuberculosis burden requires neutralising long-standing infections[2]—a more daunting task given global estimates that nearly a quarter of all people have been infected with *Mycobacterium tuberculosis*.[3]

Prevailing wisdom is that about two-thirds of incident tuberculosis in high-burden countries reflects late progression.[4] This thinking is based on two fundamental axioms. First, the annual risk of infection with *M tuberculosis* is assumed to be relatively low—between 0·5% and 2% in most high-burden countries.[3,5–7] Second, *M tuberculosis* infection is generally conceptualised as a lifelong state of elevated tuberculosis risk (called latent tuberculosis infection).[8] Under this thinking, one might assume the following for a typical high-burden country with tuberculosis incidence of 200 per 100 000: (1) 1% annual risk of infection, (2) 5% rapid progression from infection to tuberculosis disease,[9,10] (3) 30% latent tuberculosis infection prevalence,[11] and (4) 0·05% annual late progression rate (ie, approximately 5% risk over 100 years).[12] Under these assumptions, recent infection would account for only a quarter of all incident cases: 1%×5%=50 cases per 100 000 population per year versus 30%×0·05%=150 per 100 000 population per year from remote infection. This fraction would be even lower after accounting for treatment failures and relapses.

Both historical and emerging evidence[13–16] challenge the second axiom and suggest that late progression (assumption four) occurs at a much lower rate.[17] If the annual risk of infection (assumption one) were correspondingly higher, our understanding of tuberculosis in high-burden countries would be recast as a disease primarily reflecting recent, rather than remote, transmission.

Contemporary annual risk of infection estimates

Current annual risk of infection estimates are primarily derived from cross-sectional tuberculin skin test (TST) or interferon-gamma release assay (IGRA) surveys—often among children of primary school age (ie, those aged 5–12 years), though sometimes in older populations.[5] Classically, the annual risk of infection is estimated as (TST/IGRA positivity)/(age).[6,18] Thus, for example, 6% TST or IGRA positivity in 6-year-olds would equal 1% estimated annual risk of infection (assuming constant annual risk of infection for 6 years). This classical formula has been updated[5] to account for exponential decline in TST/IGRA negativity over time: annual risk of infection=$1-(1-\text{TST/IGRA positivity})^{1/\text{mean age}}$. This updated formula has been used for the majority of recent population-based annual risk of infection estimates (appendix pp 2–5) and gives very similar results to the prevailing formula when TST or IGRA positivity in the study population is less than 20%. More nuanced estimation methods exist[19,20] but require additional assumptions and are not widely used.

Such surveys in most high-burden countries have generally yielded annual risk of infection estimates between 0·5% and 2%[3,6]—consistent with an estimated 25% prevalence of *M tuberculosis* infection.[11] For example, figure 1 illustrates the population structure[21] and projected tuberculosis status by age in India under prevailing annual risk of infection estimates (ie, 1·5% in 2002 and 1·0% in 2010) based on cross-sectional TST surveys.[22] In this scenario, 75% of incident tuberculosis

See Online for appendix

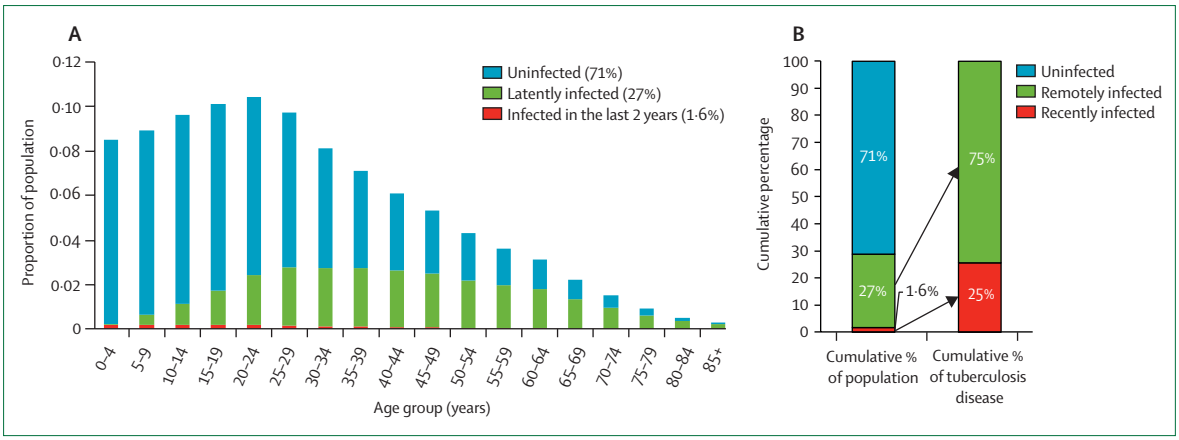


Figure 1: **Prevailing conceptualisation of *Mycobacterium tuberculosis* infection and tuberculosis**
(A) Depicts the population structure of India in 2016,[21] according to tuberculosis infection status, assuming a 1·5% annual risk of infection with *M tuberculosis* until 2005, falling to 1·0% thereafter.[22] (B) Shows the corresponding cumulative percentages of the population (left) and ensuing hazard of incident tuberculosis (right), assuming a 4% risk of disease in each of the first 2 years following infection (similar to the estimated 3·8% risk in the first year following infection currently in the USA)[15] and the remainder of disease occurring among those remotely infected to achieve the estimated incidence of tuberculosis in India (211 per 100 000 population per year).[23] The estimation presented in this figure required an assumption of 0·6% annual risk of progression among individuals with remote (ie, >2 years ago) infection—approximately six times the risk seen among long-term immigrants in Australia.[14] The fraction infected in the last 2 years is less than 2% (1% × 2 years) as the calculation assumes 77% protection from reinfection following initial infection,[24] following Houben and Dodd.[3]

reflects late progression, consistent with the previously mentioned assumptions.

Are we underestimating the annual risk of infection among adults in high-burden countries?

There are at least three ways in which the estimated annual risk of infection (ie, from TST or IGRA positivity in young children) can underestimate the true annual risk of infection—defined here as the average annual rate at which previously uninfected adolescents and adults in a population experience sufficient exposure to *M tuberculosis* to evoke a systemic T-cell-mediated response. First, children might experience a much lower risk of infection than older adolescents and adults (ie, those aged 15 years and older). Second, some people will not convert TST or IGRA responses despite intense exposure (ie, resistant immune phenotype). Third, cross-sectional surveys will overlook transient immune responses to infection. When combined, these biases can cause underestimation of the true annual risk of infection by a factor of five to ten (figure 2).

Young children have lower exposure than adolescents and adults

Annual risk of infection estimates from TST or IGRA surveys in children are often extrapolated to the full population.[5,6] However, tuberculosis is less common and less highly infectious (eg, smear-positive pulmonary tuberculosis) in children.[25,26] Thus, school-aged children—who have fewer respiratory contacts than adults and whose contacts are often other children[27–29]—should experience a lower risk of *M tuberculosis* infection than adolescents and adults. This concept is shown in population-wide TST or IGRA surveys. For example, figure 3 shows TST positivity in a single (ie, 1972–73) birth cohort across serial surveys in South Korea (between 1975 and 1995).[30] The estimated annual risk of infection in this cohort was 2·0% for ages 2·5–7·5 years, 5·1% for ages 7·5–12·5 years, and 11·8% for ages 12·5–17·5 years—when nationwide incidence was declining. Thus, if TST positivity in 5-year-olds were used to estimate population-wide annual risk of infection, the true annual risk of infection in 15-year-olds would be underestimated by a factor of six. Cross-sectional data from the Philippines[31] and South Africa[32] corroborate this trend. Indeed, we are unaware of any data suggesting a lower annual risk of infection among adolescents or young adults than among young children. The preponderance of data, therefore, suggests that, in most high-burden settings, the annual risk of infection for young children underestimates the annual risk of infection for adolescents and adults by a factor of two to six.

Some people are resistant to TST or IGRA conversion

Data published in 2019 suggest that perhaps 20% of people have a resistant immune phenotype, meaning they do not convert TST or IGRA results despite intense exposure to *M tuberculosis*.[33,34] This phenotype often appears as a ceiling effect in which TST or IGRA positivity plateaus around 80% (figure 3). Ignoring these individuals can generate substantial bias in annual risk of infection estimates that is greater than just a factor of 1·2. For example, consider adolescents ages 12·5 and 17·5 years in figure 3, of whom 64% start as TST-negative. If 20% have a resistant phenotype, then only 44% are truly susceptible to conversion. This bias causes the

annual risk of infection to be underestimated by nearly half using standard calculations (eg, 9% *vs* 13%), and by more (12% *vs* 21%) using (exponential) calculations that account for continued depletion of susceptible individuals over the 5-year period.

Some immune responses are transient

A study in South African adolescents[35] estimated that 13% of positive IGRA results revert to negative each year. At this rate, a cross-sectional survey in 7-year-old children could misclassify over one-third of all children experiencing IGRA conversion (ie, average infection at 3·5 years) as IGRA-negative—and underestimate the annual risk of infection to the same degree. TST reversions have been documented at similar rates historically.[36] In low-burden settings, transient conversions will often represent false-positives.[37] But in settings of ongoing transmission, these conversions could reflect true infections that are subsequently cleared[17,38,39]—a hypothesis supported by substantially higher conversion rates among health-care workers in high-burden countries than in low-burden countries.[40] In South Africa,[35] adolescents whose IGRA result reverted were at increased risk of tuberculosis (ie, compared to those who remained persistently negative), and annual risk of infection estimates as high as 14% were considered consistent with IGRA data. Similarly, in rural China,[41] the annual risk of infection was estimated at 1·5% using traditional calculations, but IGRA conversion occurred at 2–5% per year (and TST conversion at 8–15% per year); conversion rates also increased with age. These findings suggest that, by missing transient immune responses, cross-sectional TST or IGRA studies could underestimate the risk of infection by one-third or more.

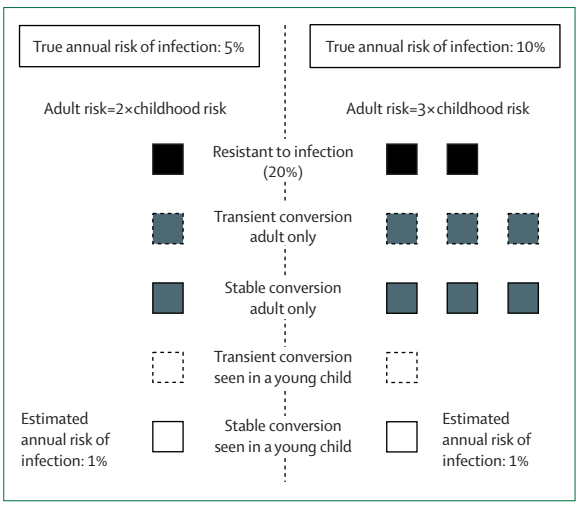


Figure 2: **Sources of potential bias in estimating the annual risk of infection with *Mycobacterium tuberculosis***

Each box represents a 1% true annual risk of infection among adults (ie, those 15 years and older) in a high-burden setting. On the left panel, assuming a 5% true annual risk of infection and a two-fold higher level of exposure among adults than among children (ie, those 12 years and younger), one-fifth of infections in adults would occur in individuals with an immune-resistant phenotype (black box). Of the remaining four infections among adults, two would not be experienced by children (owing to their 50% exposure level, grey boxes). Of the remaining two infections among adults, one might result in transient conversion of a tuberculin skin test or interferon-gamma release assay and would therefore be missed in a cross-sectional tuberculin skin test or interferon-gamma release assay survey of school-aged children (dotted boxes). Thus, a 5% true annual risk of infection in adults would be consistent with a 1% estimated annual risk of infection in such a survey. The right-hand panel illustrates how a 10% true annual risk of infection in adults could similarly be consistent with a 1% estimated annual risk of infection in a cross-sectional survey of schoolchildren under the assumption of three-fold higher exposure among adults than children. Notably, these estimates assume that all three sources of bias function independently; any overlap (for example, changing prevalence of immune-resistant phenotype with age) could increase or decrease the level of bias.

Three biases combined

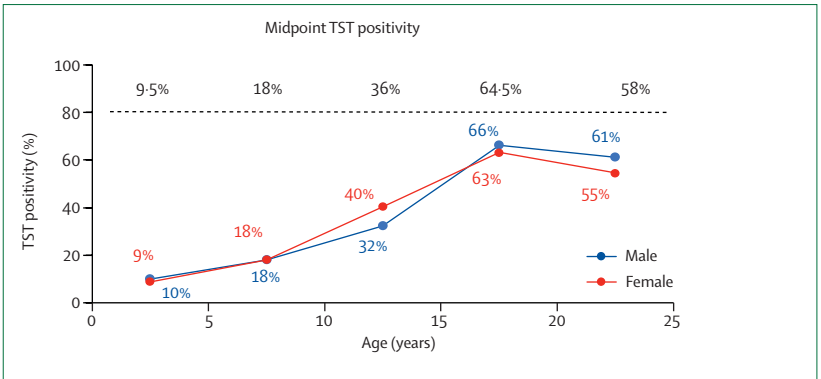
Taken together, these three biases can cause prevailing annual risk of infection estimates to underestimate the true annual risk of infection by a factor of 5–10 (figure 2). This heuristic estimate can be replicated in figure 3,[30] in which the estimated annual risk of infection among children 2·5–7·5 years old was 2·0%. Between ages 12·5 and 17·5 years, TST positivity increased from 36% to 64·5%—a 28·5 percentage point increase. Since 64% of the population was TST-negative at age 12·5, 45% of the eligible population (ie, 0·285/0·64×100) converted their TST over 5 years, equivalent to an 11·8% annual risk of infection. But if 20% of the population had a resistant phenotype, then 65% of the susceptible population (ie, 0·285/[0·64–0·2]×100) would have converted over 5 years—equivalent to a 21·1% annual risk of infection, more than 10-fold higher than the originally estimated 2·0%. Accounting for transient immune responses would increase the annual risk of infection in adolescents even further.

In summary, if one considers that (1) exposure in adolescents and adults is probably at least two to three times more intense than in young children, (2) 20% of individuals are resistant to TST or IGRA conversion under most modern levels of exposure, and (3) more than one-third of all TST or IGRA conversions could revert to negative in under 4 years—then an estimated 1% annual risk of infection from cross-sectional TST or IGRA surveys in young children is consistent with a true 5–10% (or higher) annual risk of infection in adolescents and adults.

Further evidence of a high annual risk of infection

Data used to estimate the annual risk of infection among young children could underrepresent the true annual risk of infection among adolescents and adults. But do other data suggest a true annual risk of infection that is higher than 1%? At least three pieces of evidence point in this direction.

First, the annual risk of TST conversion among adult residents of low-burden countries who travel to high-burden countries has been estimated at 4%.[42] Travellers



Age group (years)	2·5–7·5		7·5–12·5		12·5–17·5		
Assumed resistant population	None	0·2	None	0·2	None	0·2	
(A) Susceptible at start of period (1 – TST Positive-Resistant)	0·905	0·705	0·82	0·62	0·64	0·44	Estimated annual risk of infection in young children assuming no resistance: 2·0%
(B) % TST converted by period end	8·5%		18%		28·5%		
(C) Standard annual risk of infection=(B/A)/(5 years)	1·9%	2·4%	4·4%	5·8%	9%	13%	Estimated annual risk of infection in adolescents assuming 20% resistance: 21%
(D) Annual risk of infection based on exponential	**2·0%**	2·6%	5·1%	7·1%	12%	**21%**	

Figure 3: **How the estimated annual risk of infection with *Mycobacterium tuberculosis* in children can underrepresent the annual risk of infection in adolescents**

Shown in blue and red are TST positivity levels among individuals born in 1970–74, across serial TST surveys in South Korea conducted from 1975 to 1995.[30] The midpoint between males (in blue) and females (in red) is shown at the top of the graph. The table illustrates how the estimated annual risk of infection would be calculated in each of three age groups—from 2·5 to 7·5 years, from 7·5 to 12·5 years, and from 12·5 to 17·5 years—under the assumption of no immune resistant phenotype versus an assumption that 20% of the population (denoted by the horizontal dotted line) have such a phenotype and will not convert a TST response, even following sufficient exposure to generate infection in others. This figure illustrates how an apparently linear increase in TST positivity can mask substantial underestimation of the annual risk of infection among older age groups owing to depletion of the denominator of individuals susceptible to conversion and how the estimated annual risk of infection in young children (assuming no resistant phenotype) can therefore underrepresent the estimated annual risk of infection in adolescents by a factor of 10. TST=tuberculin skin test.

having a higher risk of *M tuberculosis* infection than residents themselves seems unlikely.

Second, tuberculosis incidence among people with HIV after taking tuberculosis preventive treatment is often similar to, or higher than, the estimated annual risk of infection. In the pre-antiretroviral therapy (ART) era in Zambia, tuberculosis incidence after completing a course of isoniazid was 6% per year.[43] In Botswana, the corresponding risk was most likely over 3% per year.[44] Other studies in the post-ART era—for example, in South Africa (1·4%)[45] and Côte d'Ivoire (1·1%)[46]—have documented higher than 1% annual incidence of tuberculosis after tuberculosis preventive treatment completion, despite the strong effect of ART.[47] In each of these settings, the best published estimate of country-level annual risk of infection was 1–2%.[3]

Third, studies of household tuberculosis contacts suggest a higher annual risk of infection in the community than in the home (figure 4). Specifically, TST or IGRA positivity in household contacts is generally estimated to be 25 percentage points higher (ie, in absolute terms) than the latent tuberculosis infection prevalence in the surrounding population[48]—suggesting that at least 10–20% of household contacts have been infected by either the index case or a common source case. But molecular fingerprinting studies[49–51] suggest that only a minority (approximately 25%) of adult household contacts with co-prevalent tuberculosis have a fingerprint matching the index case. Since remote infection cannot account for this discrepancy (figure 4), the risk of recent infection in the community must be similar to the risk of infection by the index case (or a common source)—ie, 10–20% over 2 years or an annual risk of infection of 5–10%. These estimates are also consistent with a meta-analysis of household and community transmission among young children.[52]

Where did the concept of a low annual risk of infection originate?

Available data suggest that the annual risk of infection among adults in high-burden settings is closer to 5–10% than to 1%. So why have lower estimates been so widely accepted? One possibility is that this reflects thinking from low-burden countries—where recent infection is likely rare, and latent tuberculosis infection is often conceptualised as a persistent state of elevated tuberculosis risk. This concept is then often reinforced by misinterpretation of positive TST or IGRA results as indicating current infection rather than previous exposure.

The idea that latent tuberculosis infection represents a persistent high-risk state arguably gained momentum with trials of isoniazid preventive therapy, which noted a lasting effect of isoniazid for up to 19 years.[53] However, the greatest effect of isoniazid (ie, a 14-year risk of tuberculosis; 1·8% *vs* 4·6% with placebo) was seen among participants with inactive and untreated tuberculosis on chest x-rays at baseline. Among people with a positive TST but no radiographical evidence of tuberculosis, the 14-year progression risk was low (ie, 0·5–0·8%) and similar between groups—suggesting that infection with *M tuberculosis* does not confer a persistently high risk of progression for many years.

Two seminal articles among people with HIV in the USA helped solidify the concept of latent tuberculosis infection as a persistent state. Selwyn and colleagues[54] followed 49 people who were both HIV-positive and TST-positive in a methadone treatment programme during the pre-ART era and estimated a tuberculosis incidence of 7·9 per 100 person-years, versus 0·3 if TST-negative. Moss and colleagues[55] similarly followed 40 people who were both HIV-positive and TST-positive and experiencing homelessness in San Francisco, CA, USA and estimated a corresponding tuberculosis incidence of 4·5 per 100 person-years, versus 0·48 if TST-negative. These findings led to a general consensus that the risk of tuberculosis in a person with latent tuberculosis infection

and untreated HIV is 5–10% per year, versus 5–10% lifetime if HIV-negative.[56,57]

These studies, however, both occurred during ongoing tuberculosis outbreaks.[58,59] Thus, cases attributed to late progression could have resulted from recent transmission. Selwyn and colleagues[54] reported that 12% of participants converted their TST result over a median of 16 months, irrespective of HIV status—similar to the observed incidence of tuberculosis (ie, 7·9 per 100 person-years) in the TST-positive population. Lower tuberculosis incidence among initially TST-negative participants than among participants with a positive TST can be explained by routine provision of isoniazid to participants whose TST converted during the study.[54] Even more striking, Moss and colleagues[55] performed routine genotyping and found that five of the six HIV-positive and TST-positive cases were (non-index) members of documented genotypic clusters—and therefore explicitly linked to recent transmission, not late reactivation. Thus, in both studies, the high tuberculosis incidence among HIV-positive individuals with a positive TST is readily explained as resulting from recent transmission.

Most incident tuberculosis among people with HIV in high-burden settings, therefore, plausibly also reflects recent transmission, rather than late reactivation.[60] Similarly the greatest effect of tuberculosis preventive treatment might be to prevent progression among people who were recently (rather than remotely) infected. Thus, the historical data underpinning of the concept of latent tuberculosis infection as a state of persistently high progression risk do not, in fact, support this framing. As such, the most parsimonious explanation for tuberculosis incidence of more than 150 per 100 000 population per year in many high-burden settings[1] is that the true population annual risk of infection is closer to 5–10%, and that late progression is less common than traditionally estimated.

Implications of a higher annual risk of infection than originally estimated

A higher annual risk of infection would reframe how we understand the burden of tuberculosis infection and disease. For example, if the annual risk of infection among adolescent and adults in India was 5% (figure 5), one might estimate that 46% of the population was ever-infected with *M tuberculosis*, 20% had a resistant immune phenotype, and only 34% was never-infected—rather than citing a 29% overall prevalence of *M tuberculosis* infection. Even more notable, more than 70% of incident tuberculosis would arise not from the large pool of people who were ever infected with *M tuberculosis*, but rather from the less than 5% of people who were infected in the past 2 years.

A higher true annual risk of infection would therefore also have implications for tuberculosis data collection, monitoring, estimation, and public health efforts. For example, estimating and monitoring the incidence of new infections (including data collection in representative cohorts) should be prioritised as an indicator of progress.

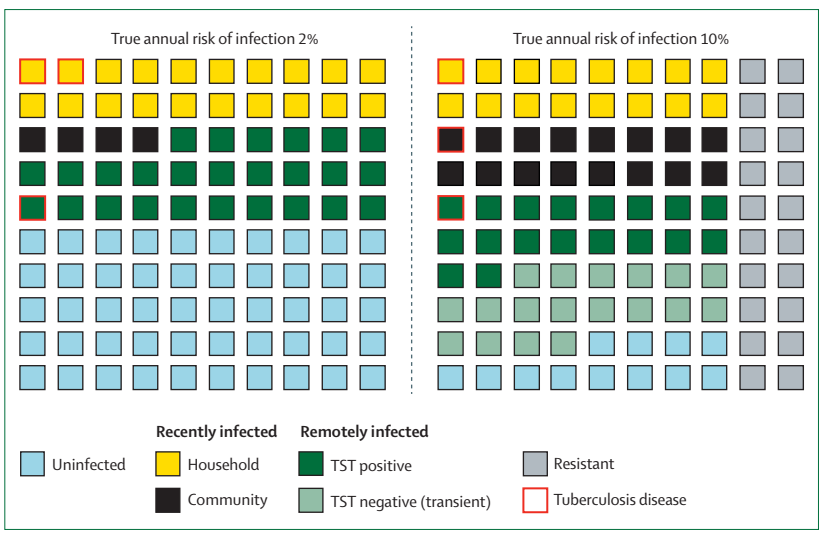


Figure 4: **Low levels of genomic concordance among household contacts are consistent with a high annual risk of infection**

For every 100 adult household contacts in high-burden countries (represented by squares), 50 are expected to be TST or IGRA positive, of whom approximately 20 are expected to be infected by either the index case or the same source as the index case (yellow squares; see section entitled, *Further evidence of a high annual risk of infection* for an explanation). Of the remaining 30, black squares represent those recently infected, and green squares represent those remotely infected. Three contacts (squares with red outlines) are expected to have co-prevalent tuberculosis.[48] The left panel shows how these data would be explained under prevailing thought, namely an assumption of 2% true annual risk of infection (assuming that household members are exposed to an annual risk of infection at the high end of the 0·5–2% range) and long-lasting latent tuberculosis infection. The right panel shows how these data would be explained under a higher 10% true annual risk of infection, as well as a 20% population with a resistant phenotype and frequent reversions of TST or IGRA responses. In the left panel, the vast majority of tuberculosis risk is seen in those exposed to the index case (or the same source as the index)—as people with recent community infection (ie, infection with the past 2 years; black squares) are rare, and those with remote latent tuberculosis infection (green squares) have a risk of progression of 1 in 10 or less. As such, the majority of household contacts with co-prevalent tuberculosis are expected to have similar genotypes to the index case. In the right panel, by contrast, household infection constitutes a smaller fraction of total risk of tuberculosis, and the majority of household contacts with co-prevalent tuberculosis are expected to have different genotypes than the index case—as is seen in observed data.[49–51] TST=tuberculin skin test. IGRA=interferon-gamma release assay.

Quantifying the population prevalence of the immune resistant phenotype would also aid more accurate estimates of the annual risk of infection from TST or IGRA surveys. Given the importance of recent infection, contact investigation—for both children and adults—should assume a higher epidemiological priority than is currently the case. Finally, recognition of a higher true annual risk of infection could engender renewed optimism, as substantial reductions in infection can be rapidly achieved (eg, from 25% to <0·1% over 20 years in the Yukon Delta, AK, USA).[61]

In making the previous arguments, certain caveats merit mention. First, this discussion pertains primarily to high-burden settings; in low-burden settings, where the annual risk of infection is already exceedingly small (<0·01%),[62] treatment of people infected at any point in their lives likely remains the only viable path toward tuberculosis elimination—though in these settings, recent infection among travelers[42] could be an underappreciated source of incident tuberculosis. Second, given the increased risk of tuberculosis in individuals with certain risk factors (eg, HIV),[63]

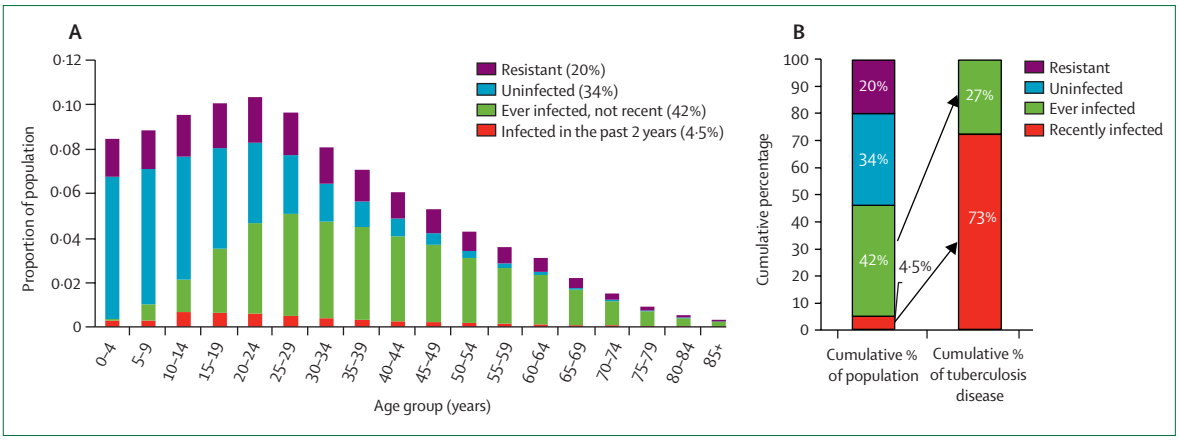


Figure 5: **Revised conceptualisation of *Mycobacterium tuberculosis* infection and tuberculosis**
(A) Depicts the population structure of India in 2016,[23] according to tuberculosis infection status, assuming a 2% annual risk of infection with *M tuberculosis* for the first 5 years of life, increasing to 5% in older age groups. (B) Shows the corresponding cumulative percentages of the population (left) and ensuing hazard of incident tuberculosis (right), assuming a 4% risk of disease in each of the first 2 years following infection (similar to the estimated 3·8% risk in the first year following infection currently in the USA)[15] and the remainder of disease occurring among those remotely infected to achieve the estimated incidence of tuberculosis in India (211 per 100 000 population per year).[23] The estimation presented in this figure required an assumption of 0·15% annual risk of progression among individuals with remote infection (ie, occurring >2 years ago)—similar to the risk seen 5–20 years after migration among long-term immigrants in Australia.[14] The fraction of those recently infected is less than 10% (5% × 2 years) as this fraction conservatively only includes individuals infected for the first time in the past 2 years (ie, that people who do not progress rapidly after an initial infection will also not progress after reinfection). To the extent that this assumption is incorrect, recent infections will account for more than 73% of all incident tuberculosis.

tuberculosis preventive treatment should remain a priority for those populations. Third, our arguments implicitly assume a homogeneously mixing population, but some settings (eg, prisons)[64] might engender higher risks of *M tuberculosis* infection than in the general population. Fourth, a substantial fraction of incident tuberculosis (14·5% in a recent cohort)[65] represents treatment failure or recurrence (primarily relapse)[66] rather than recent or remote infection per se; individuals with previously treated tuberculosis also represent a high-priority group for intervention.[67]

Conclusion

In summary, the preponderance of available evidence suggests that estimates of a 0·5–2% annual risk of infection with *M tuberculosis* in high-burden settings might underestimate the true annual risk of infection in adolescents and adults by a factor of five to ten. In high-burden countries, the majority of individuals most likely will be infected with *M tuberculosis* at some point in their lives—but more than 70% of incident tuberculosis occurs in less than 5% of the population (ie, adults infected in the past 2 years). Under this conceptualisation of tuberculosis epidemiology, key priorities should include: (1) developing assays to reliably identify individuals who have been recently infected; (2) providing people who have been recently infected with appropriate treatment; (3) implementing public health measures most likely to engage people who have been recently infected (eg, contact investigation) or interrupt recent transmission (eg, community-based case finding and prevention of infection vaccines); and (4) developing population-based data systems to monitor trends in recent infection over time.

Contributors
Both authors did the literature search. DWD wrote the first draft of the manuscript and developed the first draft of the figures. MAB revised the manuscript and added key sections. Both authors read and approved the final version of the manuscript for publication.

Declaration of interests
DWD declares no competing interests. MAB is co-owner of Patent US6291190B1, Molecular differences between species of the *Mycobacterium tuberculosis* complex, published Sept 18, 2001.

Acknowledgments
We thank Vivek Kapur, Paul Edelstein, Emily Kendall, and Lalita Ramakrishnan for their helpful comments on earlier drafts of this manuscript. This work was supported in part by a Catalyst Award from Johns Hopkins University (to DWD) and a Canada Research Chair and a Foundation Grant from the Canadian Institutes for Health Research (to MAB). The funders had no role in the writing of the manuscript or the decision to submit for publication.

References

1 WHO. Global tuberculosis report 2021. Geneva: World Health Organization, 2021.
2 Dye C, Glaziou P, Floyd K, Raviglione M. Prospects for tuberculosis elimination. *Annu Rev Public Health* 2013; **34:** 271–86.
3 Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLoS Med* 2016; **13:** e1002152.
4 Rangaka MX, Cavalcante SC, Marais BJ, et al. Controlling the seedbeds of tuberculosis: diagnosis and treatment of tuberculosis infection. *Lancet* 2015; **386:** 2344–53.
5 Rieder H. Annual risk of infection with *Mycobacterium tuberculosis*. *Eur Respir J* 2005; **25:** 181–85.
6 Cauthen GM, Pio A, ten Dam HG. Annual risk of tuberculous infection. 1988. *Bull World Health Organ* 2002; **80:** 503–11.
7 Dye C, Garnett GP, Sleeman K, Williams BG. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. *Lancet* 1998; **352:** 1886–91.
8 Shah M, Dorman SE. Latent tuberculosis infection. *N Engl J Med* 2021; **385:** 2271–80.

9 Styblo K. The relationship between the risk of tuberculous infection and the risk of developing infectious tuberculosis. *Bull Int Union Tuberc Lung Dis* 1985; **60:** 117–19.

10 Dye C. Breaking a law: tuberculosis disobeys Styblo's rule. *Bull World Health Organ* 2008; **86:** 4.

11 Cohen A, Mathiasen VD, Schön T, Wejse C. The global prevalence of latent tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2019; **54:** 1900655.

12 Horsburgh CR Jr, O'Donnell M, Chamblee S, et al. Revisiting rates of reactivation tuberculosis: a population-based approach. *Am J Respir Crit Care Med* 2010; **182:** 420–25.

13 Verver S, Warren RM, Munch Z, et al. Proportion of tuberculosis transmission that takes place in households in a high-incidence area. *Lancet* 2004; **363:** 212–14.

14 Dale KD, Trauer JM, Dodd PJ, Houben RMGJ, Denholm JT. Estimating long-term tuberculosis reactivation rates in Australian migrants. *Clin Infect Dis* 2020; **70:** 2111–18.

15 Menzies NA, Swartwood N, Testa C, et al. Time since infection and risks of future disease for individuals with *Mycobacterium tuberculosis* infection in the United States. *Epidemiology* 2021; **32:** 70–78.

16 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:** 183–201.

17 Behr MA, Edelstein PH, Ramakrishnan L. Is *Mycobacterium tuberculosis* infection life long? *BMJ* 2019; **367:** l5770.

18 Pai M, Dendukuri N, Wang L, Joshi R, Kalantri S, Rieder HL. Improving the estimation of tuberculosis infection prevalence using T-cell-based assay and mixture models. *Int J Tuberc Lung Dis* 2008; **12:** 895–902.

19 Hamaguchi Y, Yamaguchi T, Nishiura H. Estimating the annual risk of tuberculosis infection in Japan from interferon-gamma release assay data. *J Theor Biol* 2019; **460:** 125–33.

20 Houben RM, Sumner T, Grant AD, White RG. Ability of preventive therapy to cure latent *Mycobacterium tuberculosis* infection in HIV-infected individuals in high-burden settings. *Proc Natl Acad Sci USA* 2014; **111:** 5325–30.

21 Ministry of Home Affairs, Government of India. 2016 India census: statistical report. 2016. http://www.censusindia.gov.in/vital_statistics/SRS_Report_2016/9.SRS%20Statistical%20Report-Detailed%20tables-2016.pdf (accessed Dec 22, 2021).

22 Chadha VK, Sarin R, Narang P, et al. Trends in the annual risk of tuberculous infection in India. *Int J Tuberc Lung Dis* 2013; **17:** 312–19.

23 WHO. Global tuberculosis report. 2021. https://www.who.int/teams/global-tuberculosis-programme/data (accessed Dec 22, 2021).

24 Andrews JR, Noubary F, Walensky RP, Cerda R, Losina E, Horsburgh CR. Risk of progression to active tuberculosis following reinfection with *Mycobacterium tuberculosis*. *Clin Infect Dis* 2012; **54:** 784–91.

25 Marais BJ, Obihara CC, Warren RM, Schaaf HS, Gie RP, Donald PR. The burden of childhood tuberculosis: a public health perspective. *Int J Tuberc Lung Dis* 2005; **9:** 1305–13.

26 Dodd PJ, Gardiner E, Coghlan R, Seddon JA. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. *Lancet Glob Health* 2014; **2:** e453–59.

27 McCreesh N, Morrow C, Middelkoop K, Wood R, White RG. Estimating age-mixing patterns relevant for the transmission of airborne infections. *Epidemics* 2019; **28:** 100339.

28 Wallinga J, Teunis P, Kretzschmar M. Using data on social contacts to estimate age-specific transmission parameters for respiratory-spread infectious agents. *Am J Epidemiol* 2006; **164:** 936–44.

29 Mossong J, Hens N, Jit M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. *PLoS Med* 2008; **5:** e74.

30 Neuenschwander BE, Zwahlen M, Kim SJ, Engel RR, Rieder HL. Trends in the prevalence of infection with *Mycobacterium tuberculosis* in Korea from 1965 to 1995: an analysis of seven surveys by mixture models. *Int J Tuberc Lung Dis* 2000; **4:** 719–29.

31 Tupasi TE, Radhakrishna S, Pascual ML, et al. BCG coverage and the annual risk of tuberculosis infection over a 14-year period in the Philippines assessed from the Nationwide Prevalence Surveys. *Int J Tuberc Lung Dis* 2000; **4:** 216–22.

32 Middelkoop K, Bekker LG, Liang H, et al. Force of tuberculosis infection among adolescents in a high HIV and TB prevalence community: a cross-sectional observation study. *BMC Infect Dis* 2011; **11:** 156.

33 Stein CM, Nsereko M, Malone LL, et al. Long-term stability of resistance to latent *Mycobacterium tuberculosis* infection in highly exposed tuberculosis household contacts in Kampala, Uganda. *Clin Infect Dis* 2019; **68:** 1705–12.

34 Lu LL, Smith MT, Yu KKQ, et al. IFN-γ-independent immune markers of *Mycobacterium tuberculosis* exposure. *Nat Med* 2019; **25:** 977–87.

35 Andrews JR, Hatherill M, Mahomed H, et al. The dynamics of QuantiFERON-TB gold in-tube conversion and reversion in a cohort of South African adolescents. *Am J Respir Crit Care Med* 2015; **191:** 584–91.

36 Adams JM, Kalajan VA, Mork BO, Rosenblatt M, Rothrock WJ, O'Loughlin BJ. Reversal of tuberculin reaction in early tuberculosis. *Dis Chest* 1959; **35:** 348–56.

37 Dorman SE, Belknap R, Graviss EA, et al. Interferon-γ release assays and tuberculin skin testing for diagnosis of latent tuberculosis infection in healthcare workers in the United States. *Am J Respir Crit Care Med* 2014; **189:** 77–87.

38 Behr MA, Edelstein PH, Ramakrishnan L. Revisiting the timetable of tuberculosis. *BMJ* 2018; **362:** k2738.

39 Emery JC, Richards AS, Dale KD, et al. Self-clearance of *Mycobacterium tuberculosis* infection: implications for lifetime risk and population at-risk of tuberculosis disease. *Proc Biol Sci* 2021; **288:** 20201635.

40 Zwerling A, van den Hof S, Scholten J, Cobelens F, Menzies D, Pai M. Interferon-gamma release assays for tuberculosis screening of healthcare workers: a systematic review. *Thorax* 2012; **67:** 62–70.

41 Gao L, Bai L, Liu J, et al. Annual risk of tuberculosis infection in rural China: a population-based prospective study. *Eur Respir J* 2016; **48:** 168–78.

42 Cobelens FG, van Deutekom H, Draayer-Jansen IW, et al. Risk of infection with *Mycobacterium tuberculosis* in travellers to areas of high tuberculosis endemicity. *Lancet* 2000; **356:** 461–65.

43 Mwinga A, Hosp M, Godfrey-Faussett P, et al. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. *AIDS* 1998; **12:** 2447–57.

44 Samandari T, Agizew TB, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; **377:** 1588–98.

45 Churchyard G, Cárdenas V, Chihota V, et al. Annual tuberculosis preventive therapy for persons with HIV infection: a randomized trial. *Ann Intern Med* 2021; **174:** 1367–76.

46 Danel C, Moh R, Gabillard D, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med* 2015; **373:** 808–22.

47 Golub JE, Saraceni V, Cavalcante SC, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS* 2007; **21:** 1441–48.

48 Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2013; **41:** 140–56.

49 Buu TN, van Soolingen D, Huyen MN, et al. Tuberculosis acquired outside of households, rural Vietnam. *Emerg Infect Dis* 2010; **16:** 1466–68.

50 Verver S, Warren RM, Munch Z, et al. Proportion of tuberculosis transmission that takes place in households in a high-incidence area. *Lancet* 2004; **363:** 212–14.

51 Becerra MC, Huang CC, Lecca L, et al. Transmissibility and potential for disease progression of drug resistant *Mycobacterium tuberculosis*: prospective cohort study. *BMJ* 2019; **367:** l5894.

52 Martinez L, Shen Y, Mupere E, Kizza A, Hill PC, Whalen CC. Transmission of *Mycobacterium tuberculosis* in households and the community: a systematic review and meta-analysis. *Am J Epidemiol* 2017; **185:** 1327–39.

53 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:** 827–30.

54 Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Engl J Med* 1989; **320:** 545–50.

55 Moss AR, Hahn JA, Tulsky JP, Daley CL, Small PM, Hopewell PC. Tuberculosis in the homeless. A prospective study. *Am J Respir Crit Care Med* 2000; **162:** 460–64.

56 Aaron L, Saadoun D, Calatroni I, et al. Tuberculosis in HIV-infected patients: a comprehensive review. *Clin Microbiol Infect* 2004; **10:** 388–98.

57 Raviglione MC, Harries AD, Msiska R, Wilkinson D, Nunn P. Tuberculosis and HIV: current status in Africa. *AIDS* 1997; **11** (suppl B)**:** S115–23.

58 Alland D, Kalkut GE, Moss AR, et al. Transmission of tuberculosis in New York City. An analysis by DNA fingerprinting and conventional epidemiologic methods. *N Engl J Med* 1994; **330:** 1710–16.

59 Small PM, Hopewell PC, Singh SP, et al. The epidemiology of tuberculosis in San Francisco. A population-based study using conventional and molecular methods. *N Engl J Med* 1994; **330:** 1703–09.

60 Daley CL, Small PM, Schecter GF, et al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. An analysis using restriction-fragment-length polymorphisms. *N Engl J Med* 1992; **326:** 231–35.

61 Kaplan GJ, Fraser RI, Comstock GW. Tuberculosis in Alaska, 1970. The continued decline of the tuberculosis epidemic. *Am Rev Respir Dis* 1972; **105:** 920–26.

62 Sutherland I, Bleiker MA, Meijer J, Styblo K. The risk of tuberculous infection in The Netherlands from 1967 to 1979. *Tubercle* 1983; **64:** 241–53.

63 Yanes-Lane M, Ortiz-Brizuela E, Campbell JR, et al. Tuberculosis preventive therapy for people living with HIV: a systematic review and network meta-analysis. *PLoS Med* 2021; **18:** e1003738.

64 Mabud TS, de Lourdes Delgado Alves M, Ko AI, et al. Evaluating strategies for control of tuberculosis in prisons and prevention of spillover into communities: an observational and modeling study from Brazil. *PLoS Med* 2019; **16:** e1002737.

65 Mave V, Chen L, Ranganathan UD, et al. Whole genome sequencing assessing impact of diabetes mellitus on tuberculosis mutations and type of recurrence in India. *Clin Infect Dis* 2022; published online Jan 4. https://doi.org/10.1093/cid/ciab1067.

66 Shanmugam S, Bachmann NL, Martinez E, et al. Whole genome sequencing based differentiation between re-infection and relapse in Indian patients with tuberculosis recurrence, with and without HIV co-infection. *Int J Infect Dis* 2021; **113** (suppl 1)**:** S43–47.

67 Marx FM, Yaesoubi R, Menzies NA, et al. Tuberculosis control interventions targeted to previously treated people in a high-incidence setting: a modelling study. *Lancet Glob Health* 2018; **6:** e426–35.