Duration of effectiveness of tuberculosis preventive treatment across various tuberculosis burden settings: a systematic review and individual-participant meta-analysis

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Summary

Background Millions of individuals at risk of tuberculosis are given tuberculosis preventive treatment (TPT) annually. However, questions remain regarding the duration of protection from TPT and potential variability across populations and settings with disparate tuberculosis risk. We aimed to assess the effect of TPT on time to tuberculosis among close contacts of individuals with tuberculosis and with evidence of *Mycobacterium tuberculosis* infection across high-burden, medium-burden, and low-burden settings.

Methods In this systematic review and individual-participant meta-analysis, we searched MEDLINE, PubMed, Web of Science, BIOSIS, and Embase for cohort studies and randomised controlled trials published between Jan 1, 1998, and Aug 28, 2023. Studies were eligible if they included individuals (of any age) with household or close exposure to a person with microbiologically or clinically diagnosed tuberculosis (contacts); had at least 6 months of contact follow-up from baseline; and reported start and end of follow-up dates or days of follow-up. We pooled individual-participant data from included cohorts, including contact and index patient characteristics and setting. Analyses were restricted to participants who tested positive for *M tuberculosis* infection at baseline and stratified by background tuberculosis burden (low burden was defined as a country-level annual incidence of <20 per 100 000 population, medium as 20–100 per 100 000 population, and high as >100 per 100 000 population). The primary outcome was incident tuberculosis, which was defined as tuberculosis diagnosed more than 90 days after baseline. We calculated incidence rates by TPT status, generated Nelson–Aalen cumulative hazard plots, and estimated adjusted hazard ratios (HRs) using mixed-effects Cox models with a time interaction. This study is registered with PROSPERO, CRD42018087022.

Findings Of 466 523 participants from 47 studies, we included 84 128 individuals from 44 cohort studies across 24 countries. TPT was highly protective within the first year but declined over the course of follow-up in all settings, with greater effects observed in low-burden and medium-burden settings. At 1 year, the adjusted HR was 0·57 (95% CI 0·31–1·07) in high-burden settings, 0·14 (0·09–0·21) in medium-burden settings, and 0·21 (0·17–0·26) in low-burden settings. The protective effect persisted up to the end of follow-up in medium-burden settings (adjusted HR at 8 years 0·15 [95% CI 0·07–0·33]) and up to 13 years in low-burden settings (0·65 [0·43–1·00]). In medium-burden and low-burden settings, participants who completed TPT initially had lower risk of tuberculosis than those who did not complete TPT (adjusted HR at 1 year 0·59 [95% CI 0·36–0·95]); within 2 years, these groups were not statistically different (adjusted HR at 2 years 0·72 [0·41–1·26]) and both showed strong protection for at least 8 years.

Interpretation Among close contacts with evidence of *M tuberculosis* infection, we found that the initial protection from TPT eroded relatively quickly in high-burden settings, but was sustained long-term in medium-burden and low-burden settings. In medium-burden and low-burden settings, completing TPT provided greater initial protection, but TPT non-completers had similar long-term tuberculosis risk.

Funding None.

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Lancet Respir Med 2026

Published Online September 18, 2026 https://doi.org/10.1016/S2213-2600(26)00219-5

See Online/Comment https://doi.org/10.1016/S2213-2600(26)00278-X

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Research in context

Evidence before this study

Since tuberculosis preventive treatment (TPT) was first introduced in the 1950s, substantial evidence has consistently shown it to be highly effective at reducing the risk of developing tuberculosis in individuals infected with *Mycobacterium tuberculosis* or at high risk of disease. An early landmark trial of community-wide isoniazid TPT conducted in the 1950s among Alaska Natives showed lasting protection against tuberculosis for at least 5 years. Other early trials showed isoniazid TPT to be similarly durable. However, several studies done in the past 30 years in people with HIV and in settings with high tuberculosis burden have shown that the protection from TPT waned rapidly after medication completion, attributed to insufficient sterilisation of the initial infection, high risk of reinfection, or both. These findings have raised debate regarding the allocation of resources towards TPT compared with other interventions in high-burden settings, particularly in adults. How the duration of protection from TPT among contacts—a specific high-risk group—might vary by setting remains unclear. We searched PubMed and Google Scholar for relevant articles published from database inception to Dec 31, 2025, using the search terms "tuberculosis", "contact", "household", "preventive treatment", and "isoniazid", among others (appendix p 49). We also reviewed reference lists, bibliographies, and other narrative reviews for additional relevant articles. Several studies, including randomised controlled trials and modelling studies, were identified that evaluated the use of TPT among contacts in disparate settings. However, few articles addressed the duration of protection from TPT, particularly beyond the first 1–2 years from contact identification, and none were identified that directly compared duration of protection across different global regions.

Added value of this study

In this systematic review and meta-analysis, we used individual-level data from 44 cohort studies in 24 countries to provide estimates of the duration of protection from a course of TPT stratified by the background tuberculosis burden of the study setting. The analysis included 84 128 participants who tested positive for *M tuberculosis* infection at baseline and were followed up for 515 560 person-years, during which 1080 incident tuberculosis diagnoses were made. Using Cox models, we showed that the hazard of tuberculosis was substantially reduced at the beginning of follow-up and that this effect waned over time across settings. In high-burden settings, protection against tuberculosis waned within about a year from baseline, whereas protection was sustained for substantially longer in medium-burden settings (≥8 years) and low-burden settings (≥13 years). In medium-burden and low-burden settings, we found that completing TPT provided the greatest overall protection. However, within 2 years from baseline, the protective effect of TPT was not statistically different between TPT completers and non-completers, and individuals who did not complete TPT still had strong, long-lasting reductions in tuberculosis risk for at least 8 years (*vs* those who did not receive TPT). To our knowledge, this is the first study to provide long-term, setting-specific estimates of the duration of TPT protection among contacts infected with *M tuberculosis* using harmonised individual-level data across numerous cohorts and world regions.

Implications of all the available evidence

Our findings indicate that TPT is highly effective in preventing tuberculosis in contacts and suggest that the duration for which this protection is sustained differs by tuberculosis risk setting. In medium-burden and low-burden settings, our results in combination with existing evidence suggest that a single course of TPT for high-risk groups might yield sustained reductions in tuberculosis risk and contribute meaningfully to reducing long-term incidence. In high-burden settings, where reinfection pressure is greater, our findings show that TPT alone is unlikely to provide sustained protection beyond 1–2 years. Pairing TPT with interventions that reduce ongoing *M tuberculosis* transmission, such as increased active case finding, might be crucial to extend the effective duration of protection from TPT in higher-burden settings. Additionally, in medium-burden and low-burden settings, we found that completing TPT (as opposed to not completing all prescribed doses) provided the greatest protection against development of tuberculosis, particularly in the first 2 years after *M tuberculosis* exposure. However, in these settings, we also found that an incomplete course of TPT might still provide substantial, lasting protection, further supporting the importance of initiating TPT among high-risk groups.

Introduction

Tuberculosis is preventable.[1] There are currently several effective tuberculosis preventive treatment (TPT) regimens that substantially reduce the risk of developing tuberculosis following *Mycobacterium tuberculosis* infection.[2] Expanding TPT delivery is central to WHO's End TB Strategy, with global coverage increasing from 1 million in 2015 to 5·3 million in 2024.[3,4] At the 2023 UN high-level meeting on tuberculosis, officials set an ambitious target of providing TPT to 45 million people at high risk of progression to disease (eg, household contacts and individuals with HIV) by 2027.[5] However, crucial questions remain regarding how to prioritise TPT provision across disparate settings and populations.[1,2,6]

The effectiveness of TPT has been shown across varying populations, including people with HIV.[2,7–9] Although a course of TPT can effectively prevent progression of an existing *M tuberculosis* infection, the magnitude and duration of protection gained vary by setting, drug regimen, adherence, and patient risk factors. TPT is also not expected to confer protection against subsequent reinfection.[10] Trials in people with HIV in Botswana and Uganda and in South African gold miners showed substantially reduced tuberculosis

risk during TPT but rapid increases after treatment completion.[11–13] In these high-incidence settings, high rates of re-exposure probably drove much of the tuberculosis resurgence, although incomplete sterilisation might also have played a part; the precise biological mechanisms of the increasing risk remain unclear. By contrast, one South African trial in people with HIV reported sustained risk reduction up to 4 years,[14] and two Brazilian trials (medium-burden settings) showed long-term protective effects in populations with and without HIV.[15,16]

Previous studies examining the duration of TPT protection have had limited power because only a small proportion of individuals infected with *M tuberculosis* ultimately develop tuberculosis.[15,16] These studies have been performed in single sites or countries, and most conducted in the past 30 years restricted analyses to individuals with HIV. How these results generalise to people without HIV, who represent more than 90% of all individuals with tuberculosis globally, is unclear. Large, multi-setting longitudinal studies spanning diverse risk groups are not available but are needed to better characterise differential effectiveness and duration of TPT protection to inform global policies.[17]

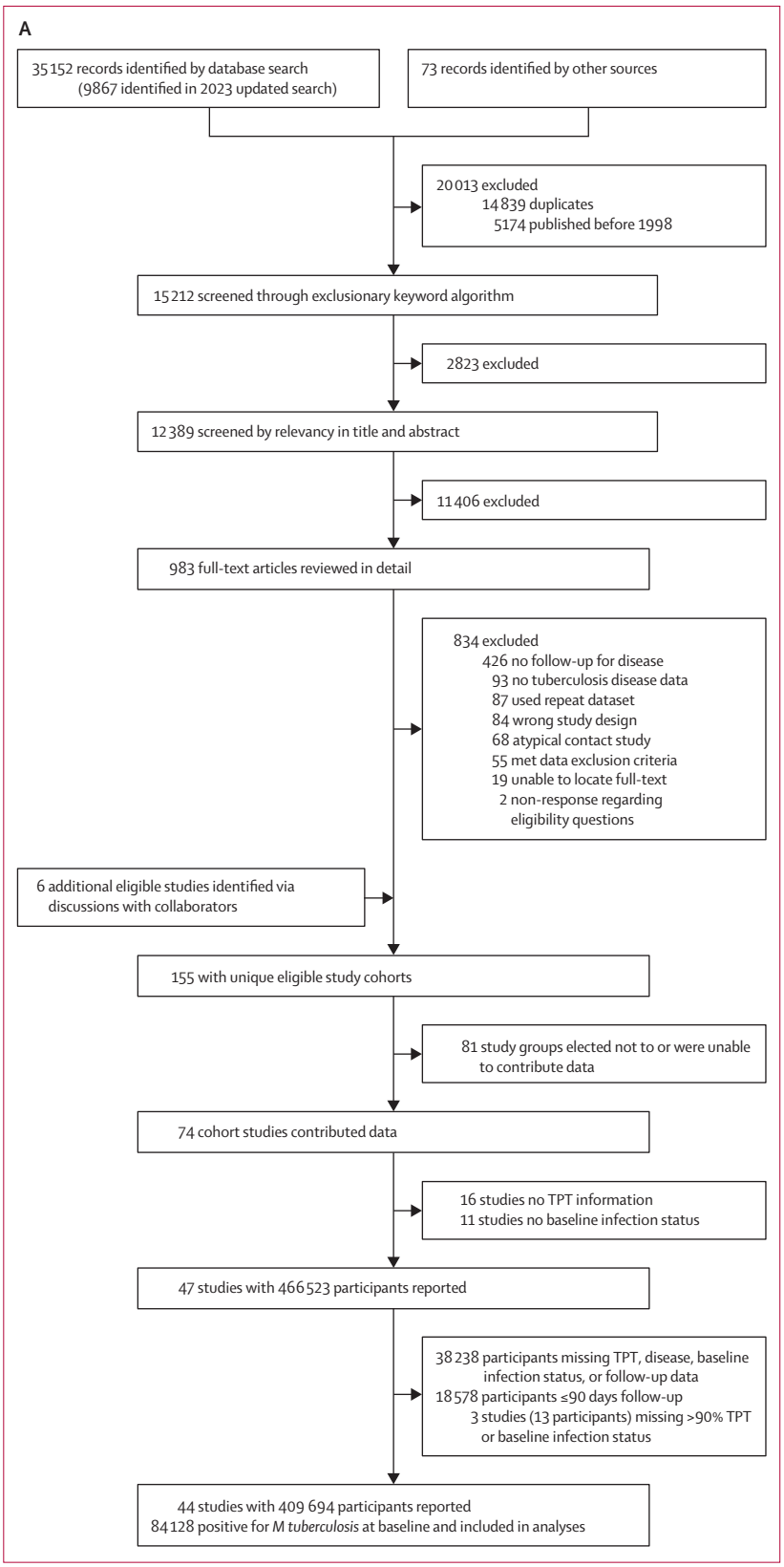
To address this gap, we assembled a large consortium of cohort studies on close contacts of patients with tuberculosis to evaluate and compare TPT effectiveness over time across settings of varying tuberculosis burden and contact risk factors, including age, HIV status, and treatment completion.

Methods

Search strategy and selection criteria

We conducted a systematic review and individual-participant meta-analysis of contact-tracing studies in two phases, as described previously.[10,18,19] The initial search covered Jan 1, 1998, to April 6, 2018, and the update covered April 7, 2018, to Aug 28, 2023. We searched MEDLINE, PubMed, Web of Science, BIOSIS, and Embase for cohort studies and randomised controlled trials with incident tuberculosis outcomes. No language restriction was applied. Owing to the broad search, we developed a list of exclusionary terms to filter irrelevant manuscripts based on titles (appendix pp 60–66). We tested these terms on 100 random titles, finding 100% specificity. Grey literature sources were also assessed. Full search details are available in the appendix (pp 26, 49–50).

We requested de-identified individual-participant data and a prespecified set of variables from the study authors of eligible cohorts, including demographic and clinical characteristics of contacts and index patients and characteristics of the setting (full list provided in the appendix, p 67). To be eligible for inclusion in the overall consortium, studies needed: individuals with household or close exposure to a person with tuberculosis (contacts); at least 6 months of contact follow-up from baseline; and



(Figure 1 continues on next page)

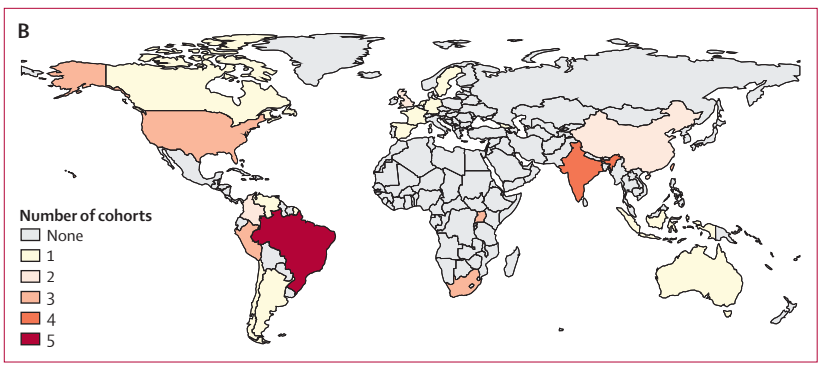


Figure 1: **Study selection (A) and geographical distribution of included studies (B)**
Excluded full-text articles and participants might have had more than one reason for exclusion, but only one reason for exclusion was listed for each excluded manuscript or participant. TPT=tuberculosis preventive treatment.

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start and end of follow-up dates or days of follow-up. We included all age groups and contacts of index patients with drug-resistant and those with drug-susceptible tuberculosis. We excluded participants missing TPT data, baseline *M tuberculosis* infection status, disease status, follow-up time, or with 90 days or less of follow-up from the study baseline. Two reviewers independently assessed the quality of each study (LRL, LM, or JIC) using a modified Newcastle–Ottawa scale (appendix pp 27, 43–48).[20] The protocol followed PRISMA-IPD guidelines (appendix pp 51–54) and was registered with PROSPERO (CRD42018087022); the Boston University Medical Campus (Boston, MA, USA) Institutional Review Board determined the work to be exempt (H-44818).

We pooled individual-participant data from included cohorts. Participants were defined as individuals with reported household or close contact to a person with microbiologically or radiologically diagnosed tuberculosis. We used the contact and index patient definitions provided by each study (appendix pp 28–36). *M tuberculosis* infection was defined as a positive QuantiFERON (Qiagen, Hilden, Germany) test (interferon-γ minus nil value ≥0·35 IU/mL), enzyme-linked immunosorbent spot test (more than eight spot-forming cells per well), or tuberculin skin test (≥10 mm induration). Preventive treatment regimen and duration were assigned per study protocols or local guidelines and practices. Searches were conducted by LM and JIC.

Data analysis

Our primary outcome was incident tuberculosis. To minimise misclassification of prevalent disease as incident, we defined incident tuberculosis as tuberculosis diagnosed more than 90 days after baseline based on a previous systematic review of contact studies that found co-prevalent tuberculosis was typically diagnosed within 3 months of the index case's diagnosis.[21] Therefore, our follow-up (time zero) began at 90 days after baseline (including for all incidence calculations and statistical models), and participants were followed up until tuberculosis diagnosis, loss to follow-up, death, or study completion. The baseline timepoint for each study was the initial contact evaluation or the start of TPT. Tuberculosis case definitions and diagnostic algorithms were provided by each study, including at baseline versus follow-up evaluations; studies included a mix of laboratory-confirmed and clinical diagnoses (appendix pp 32–42).

We primarily aimed to assess differences in the time to development of tuberculosis between contacts who did versus did not initiate TPT. To reduce confounding by indication, analyses were restricted to contacts testing positive for *M tuberculosis* infection at baseline. For participants with both baseline interferon gamma release assay and tuberculin skin test results available, we accepted a positive result from either test. Our primary analysis was conducted as intention to treat, meaning that we assessed receipt of (rather than adherence to or documented completion of) TPT.

We calculated tuberculosis incidence rates (cases per 1000 person-years) by participant characteristics and generated Nelson–Aalen cumulative hazard plots. We fitted Cox proportional hazards regression models adjusted for age, sex, and background tuberculosis burden, with random effects for the study and study design (prospective *vs* retrospective). We did not control for HIV status in the primary models due to data missingness.

All models were stratified by category of background tuberculosis burden, which was defined by the incidence rate in terms of annual number of tuberculosis cases diagnosed per 100 000 population in the country where the study took place. Country-level annual tuberculosis incidence rates were obtained from WHO. Low burden was defined as less than 20 average annual cases per 100 000 population, medium burden as 20–100 average annual cases per 100 000 population, and high burden as more than 100 average annual cases per 100 000 population.[21] Background burden was assigned based on the year of the baseline contact evaluation date if known and the midpoint of the study period if unknown. Models were further stratified by age group (<5 years, 5–14 years, 15–44 years, and ≥45 years), TPT completion status (complete *vs* incomplete), and TPT regimen, controlling for the same set of covariates as the primary models. In all time-to-event analyses, we limited the follow-up time to the nearest whole year by which at least 99% of all participants in either exposure group (TPT or no TPT) had ended follow-up; this corresponded to 3 years in high-burden, 8 years in medium-burden, and 20 years in low-burden settings.

Models were first fitted using the full available follow-up time, as described previously, then in increasing follow-up durations—from baseline to 1 year, then up to 2 years, 3 years, 4 years, 10 years, and 20 years, as available by burden category—to assess how estimates changed with increasing follow-up duration. The proportional hazards

assumption was tested using Schoenfeld residuals. Each of these initial models violated the proportional hazards assumption. Therefore, we incorporated an interaction term with follow-up time to explicitly model the changing hazard ratios (HRs).[22,23] Finally, in a secondary analysis, we fitted Cox models in non-cumulative increments of 1 year in length up to 4 years (year-specific rates), then 4–10 years and 10–20 years.

We conducted several prespecified sensitivity analyses. First, we limited the sample to studies with at least 8 years of follow-up in medium-burden and low-burden settings to assess for the potential influence of studies with shorter follow-up that might have systematic differences in longer-term tuberculosis risk. Second, we assessed different exclusion thresholds to account for prevalent tuberculosis at the start of follow-up, including 30 days, 60 days, and 180 days (90 days being our primary analysis). Third, we conducted a leave-one-out analysis, removing each study sequentially from the sample to assess individual study influence. Finally, because 19 studies (43%, representing 15% of participants) were completely missing HIV data, we evaluated several approaches to adjust for HIV, including complete case analysis, selective imputation, and multiple imputation (appendix p 18).

Role of the funding source

There was no funding source for this study.

Results

We identified 466 523 participants from 47 cohort studies (appendix pp 55–59). After excluding individuals with insufficient follow-up or missing data, 409 694 participants from 44 cohort studies in 24 countries (1·6 million person-years) were eligible for inclusion (figure 1; appendix pp 3–5). Of these participants, 84 128 tested positive for *M tuberculosis* infection at baseline (44 182 [52·5%] took TPT) and were included in the final analytical population (figure 1). These participants were followed up for 515 560 person-years, during which 1080 incident tuberculosis diagnoses were made. 17 (38·6%) of 44 studies were deemed to be of moderate quality and 24 (54·5%) of high quality.

27 (61·4%) of 44 studies comprised fewer than 1000 individuals, and participants were treated with a TPT regimen of 6 months or 9 months of isoniazid in 28 (90·3%) of 31 studies that reported regimens (table 1). In medium-burden and high-burden settings, almost all participants were provided an isoniazid regimen (24 754 [99·9%] of 24 787 in medium-burden settings and 2590 [97·3%] of 2661 in high-burden settings), and all participants in high-burden settings were on a TPT regimen of at least 6 months; 11 876 (78·9%) of 15 057 participants in low-burden settings were provided an isoniazid regimen (appendix pp 8–9). Studies were most commonly conducted in the region of the Americas (17 [38·6%] of 44) and most participants were from either the region of the Americas (37 001 [44·0%] of 84 128) or the Western Pacific region (36 589 [43·5%]; table 1). About a third of studies were conducted in low-burden settings

	Studies (n=44)	Participants (n=84 128)
Study design		
Retrospective	17 (38·6%)	68 110 (81·0%)
Prospective	27 (61·4%)	16 018 (19·0%)
Annual country-level tuberculosis incidence, cases diagnosed per 100 000 population		
<20 (low burden)	13 (29·5%)	38 158 (45·4%)
20–100 (medium burden)	16 (36·4%)	35 976 (42·8%)
>100 (high burden)	15 (34·1%)	9994 (11·9%)
WHO region		
African	7 (15·9%)	4049 (4·8%)
Americas	17 (38·6%)	37 001 (44·0%)
Eastern Mediterranean	0	0
European	8 (18·2%)	5649 (6·7%)
South-East Asia	5 (11·4%)	840 (1·0%)
Western Pacific	7 (15·9%)	36 589 (43·5%)
Mean follow-up, years*		
<2	22 (50·0%)	22 456 (26·7%)
2–4	14 (31·8%)	26 184 (31·1%)
≥5	8 (18·2%)	35 488 (42·2%)
Cohort size		
<1000	27 (61·4%)	4952 (5·9%)
1000–5000	10 (22·7%)	9717 (11·6%)
>5000	7 (15·9%)	69 459 (82·6%)
Number participants prescribed TPT	NA	44 182 (52·5%)
TPT regimen reported	31 (70·5%)	42 454/44 182 (96·1%)
Type of preventive treatment used†		
6 months or 9 months of isoniazid	28/31 (90·3%)	39 220/42 454 (92·3%)
4 months of rifampicin	7/31 (22·6%)	2399/42 454 (5·7%)
3 months of isoniazid and rifapentine	4/31 (12·9%)	567/42 454 (1·3%)
3 months of isoniazid and rifampin	4/31 (12·9%)	212/42 454 (0·5%)
6 months of levofloxacin	2/31 (6·5%)	5/42 454 (<0·1%)
Other regimen‡	3/31 (9·7%)	102/42 454 (0·1%)
HIV status of participants reported§	25 (56·8%)	71 846 (85·4%)

Data are n (%). Percentages might not sum to 100 as a result of rounding. NA=not applicable. TPT=tuberculosis preventive treatment. *Follow-up time is counted from baseline (not excluding the first 90 days of follow-up). †Some studies included more than one TPT regimen provided to different subsets of participants. In the study column, we tally each study that had any participants provided with each noted regimen; therefore, in the study column the total number of studies is >31 and the percentages total >100%. ‡Other regimens were ofloxacin, ethambutol, and high-dose isoniazid for 6 months in one study (71 participants) and a wide range of alternative regimens in two studies (31 participants), including 2 months of rifampin and pyrazinamide (seven participants), 2 months of rifampin and 6 months of isoniazid (four), and others (20). §Study-level information on HIV burden is available in the appendix (p 18).

Table 1: **Demographic characteristics of the included cohort studies and individual participants with a positive test for *Mycobacterium tuberculosis* infection at baseline**

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	Contacts	Median follow-up (years)	Incident tuberculosis	Total person-time (years)	Incidence rate, per 1000 person-years (95% CI)
Overall	84128	3·8 (1·6–9·2)	1080	515559·5	2·1 (2·0–2·2)
Prescribed TPT					
Yes	44182	3·2 (1·5–7·2)	205	230888·6	0·9 (0·8–1·0)
No	39946	4·5 (1·8–13·5)	875	284670·9	3·1 (2·9–3·3)
Completed TPT*					
Yes	18177	2·5 (1·3–4·7)	43	61717·1	0·7 (0·5–0·9)
No	11585	2·6 (1·1–4·6)	47	37403·8	1·3 (0·9–1·6)
Age group, years					
<5	8121	2·6 (1·4–4·0)	79	26245·4	3·0 (2·3–3·7)
5–14	20135	2·6 (1·4–4·1)	160	68403·5	2·3 (2·0–2·7)
15–44	34805	4·8 (1·6–10·6)	569	236037·2	2·4 (2·2–2·6)
≥45	20110	6·6 (2·1–15·3)	272	169460·0	1·6 (1·4–1·8)
Sex					
Female	42905	3·7 (1·6–9·4)	534	264533·8	2·0 (1·8–2·2)
Male	40766	3·8 (1·7–8·7)	544	246191·8	2·2 (2·0–2·4)
HIV status					
Negative	71345	4·0 (1·6–10·6)	847	464246·3	1·8 (1·7–1·9)
Positive	501	3·8 (1·4–16·6)	28	3976·6	7·0 (4·4–9·6)
Background tuberculosis burden†					
High	9994	0·8 (0·8–1·8)	213	14772·7	14·4 (12·5–16·4)
Medium	35976	2·2 (1·2–3·5)	331	91426·0	3·6 (3·2–4·0)
Low	38158	10·2 (5·6–16·3	536	409360·8	1·3 (1·2–1·4)

TPT=tuberculosis preventive treatment. *Completion status available for 119 (4·1%) of 2873 participants in high-burden settings, 23276 (93·2%) of 24971 participants in medium-burden settings, and 6367 (39·0%) of 16338 participants in low-burden settings. †Country-level tuberculosis incidence data were collected from WHO for each study. Background tuberculosis burden category defined by the incidence rate in terms of annual number of tuberculosis cases diagnosed per 100000 population in the country where the study took place for the year of contact evaluation or (if unknown) the midpoint of the study time period. Low burden is defined as <20 average annual tuberculosis cases diagnosed per 100000 population, medium burden as 20–100 average annual tuberculosis cases diagnosed per 100000 population, and high burden as >100 average annual tuberculosis cases diagnosed per 100000 population.

Table 2: **Follow-up time and incidence rates for tuberculosis by participant characteristics**

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(13 [29·5%]), medium-burden settings (16 [36·4%]), and high-burden settings (15 [34·1%]). Of 84128 included participants, 38158 (45·4%) were from low-burden settings, 35976 (42·8%) from medium-burden settings, and 9994 (11·9%) from high-burden settings.

1080 incident tuberculosis cases were diagnosed (incidence rate 2·1 [95% CI 2·0–2·2] per 1000 person-years) over a median follow-up time of 3·8 years (IQR 1·6–9·2; table 2). The duration of follow-up varied by study and tuberculosis burden category. Median follow-up time (from 90 days post-baseline onwards) was 0·8 years (IQR 0·8–1·8) in high-burden settings, 2·2 years (1·2–3·5) in medium-burden settings, and 10·2 years (5·6–16·3) in low-burden settings (table 2). Examining the first 2 years of follow-up (for comparability across settings), in each tuberculosis burden category, the crude incidence rate per 1000 person-years was higher in individuals who did not take TPT than in those who did, with the highest rates in high-burden settings (19·5 [95% CI 16·6–22·5] *vs* 10·5 [6·9–14·0]), followed by medium-burden settings (13·8 [11·6–14·9] *vs* 1·1 [0·8–1·4]) and low-burden settings (7·8 [7·0–8·7] *vs* 1·8 [1·3–2·3]; appendix p 7; overall crude incidence rates are available in the appendix, p 6). Most people with incident tuberculosis were diagnosed within the first 2 years of follow-up, including 284 (85·8%) of 331 participants in medium-burden settings and 383 (71·4%) of 536 in low-burden settings; follow-up time was insufficient to assess this proportion in the high-burden group.

In each tuberculosis burden category, the hazard of tuberculosis rose rapidly in the first year of follow-up in participants not prescribed TPT and rose to a lesser extent in the group that did take TPT (figure 2A; see appendix p 10 for accompanying number of events and number at risk over follow-up time). After the first year, the hazard continued to climb rapidly in the high-burden group in both TPT and non-TPT strata and increased, although at a much-reduced rate, in the medium-burden and low-burden groups. In the medium-burden and low-burden groups, the cumulative hazards remained substantially higher in the non-TPT group than in the TPT group over the full course of follow-up.

Similar trends were reflected in modelling the HRs using a time-interaction term (figure 2B). Across all burden categories, the adjusted HRs indicated that TPT provided strong protection at the beginning of follow-up, which decreased rapidly within the first year before flattening. At 90 days (when most participants were still on or just concluding their course of TPT, except for 3252 [21·6%] of 15057 participants in low-burden settings who took a regimen shorter than 6 months), the adjusted HR was 0·44 (95% CI 0·27–0·74) in high-burden settings, 0·13 (0·09–0·18) in medium-burden settings, and 0·11 (0·08–0·16) in low-burden settings (figure 2). At 1 year, the adjusted HRs had increased to 0·57 (95% CI 0·31–1·07) in high-burden settings (with the 95% CIs crossing the null just before a year), 0·14 (0·09–0·21) in medium-burden settings, and 0·21 (0·17–0·26) in low-burden settings (appendix p 15). Sustained protection was observed up to at least 8 years in both medium-burden settings (adjusted HR 0·15 [95% CI 0·07–0·33]) and low-burden settings (0·53 [0·36–0·76]; appendix p 15). The protective effect continued to move gradually towards the null in the low-burden group over the remaining follow-up time up to 20 years, with 95% CIs crossing the null at about 13 years (adjusted HR 0·65 [95% CI 0·43–1·00]). In a sensitivity analysis limited to studies with at least 8 years of follow-up in medium-burden and low-burden settings, results remained consistent (appendix p 14). Overall results also remained consistent when removing each individual study in the leave-one-out sensitivity analysis and using different thresholds for the prevalent tuberculosis exclusion window (appendix p 15).

In time-interaction models stratified by age group, we observed no statistically significant differences between

groups within each setting (appendix p 11). Controlling for HIV shifted results closer to the null in high-burden settings (adjusted HR at 1 year 0·65 [95% CI 0·33–1·30]) but had minimal impact in low-burden settings (appendix p 19). Participants in medium-burden settings in our sample were overwhelmingly HIV negative, with only 15 (0·05%) of 30771 participants HIV positive. In stratified analyses, the HIV-positive subgroup had an insufficient sample size to run time-interaction models across all settings. The HIV-negative subgroups in high-burden and low-burden settings showed stronger protection from TPT in the first year of follow-up than the overall sample (appendix p 21). After 1 year, the adjusted HRs were consistent with results from the overall sample in low-burden settings and waned more rapidly towards the null in the high-burden group.

Among the 44182 participants prescribed TPT, 29762 (67·4%) had documented TPT completion information. Availability of TPT completion status varied by background burden: 119 (4·1%) of 2873 participants in high-burden settings, 23276 (93·2%) of 24971 in medium-burden settings, and 6367 (39·0%) of 16338 in low-burden settings had documented TPT completion status. Of these individuals, 18177 (61·1%) completed TPT (appendix pp 12–13).

We excluded studies from high-burden settings in subsequent analyses by TPT completion status given that these data were overwhelmingly missing, and limited these analyses to the first 8 years of follow-up to align with analyses conducted in medium-burden settings. TPT non-completers developed tuberculosis at a faster rate than those who did complete TPT (median 1·06 years [IQR 0·14–2·91] *vs* 1·86 years [0·40–4·06]). TPT completers had the lowest cumulative hazard of tuberculosis over the 8-year follow-up period, although 95% CIs overlapped with the TPT non-completers after about 3 years (figure 3). In an adjusted time-interaction Cox model, we observed stronger protection against tuberculosis in TPT completers than in non-completers for the first 1–2 years of follow-up. In a model comparing the completers with the non-completers, the adjusted HR was 0·59 (95% CI 0·36–0·95) at 1 year after baseline (appendix p 16). At 2 years after baseline, the adjusted HR was 0·72 (95% CI 0·41–1·26). We observed long-term protection against tuberculosis in both the TPT completers and the non-completers. In models comparing TPT completers and non-completers with participants who did not take TPT at all, at 1 year after baseline, adjusted HRs were 0·12 (95% CI 0·08–0·17) among TPT completers and 0·16 (0·11–0·24) among non-completers (appendix p 16). 8 years after baseline, the adjusted HRs were 0·34 (0·18–0·65) among completers and 0·19 (0·10–0·38) among non-completers, with overlapping 95% CIs.

In low-burden settings, we had a sufficient sample size to stratify by regimen for 4 months of rifampicin (4R) versus isoniazid (either 6 months or 9 months). Models

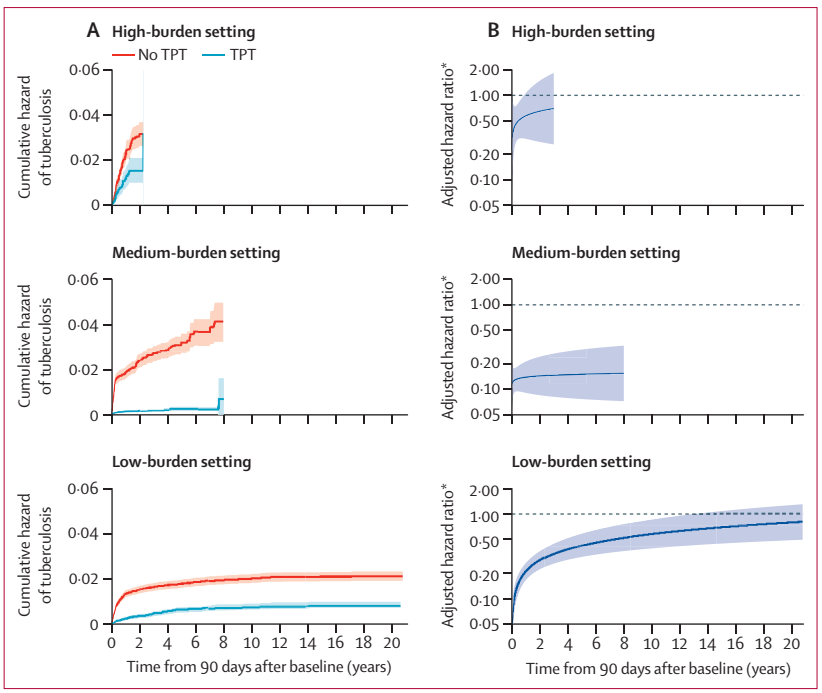


Figure 2: **Cumulative hazard plots (A) and adjusted hazard ratios of TPT against incident tuberculosis, stratified by background tuberculosis burden category (B)**

Shaded regions represent 95% CIs. Background tuberculosis burden was defined by the incidence rate in terms of annual number of tuberculosis cases diagnosed per 100 000 population in the country where the study took place in the year of the midpoint of the study time period. Low burden is defined as <20 average annual tuberculosis cases diagnosed per 100 000 population, medium burden as 20–100 average annual tuberculosis cases diagnosed per 100 000 population, and high burden as >100 average annual tuberculosis cases diagnosed per 100 000 population. TPT=tuberculosis preventive treatment. *Models adjusted for age, sex, background tuberculosis burden in the study setting as a continuous variable, with random effects at the study level and study design level and including an interaction term between TPT status and log(time). †A table of the number of participants at risk and cumulative number of events over follow-up time by burden category is available in the appendix (p 10).

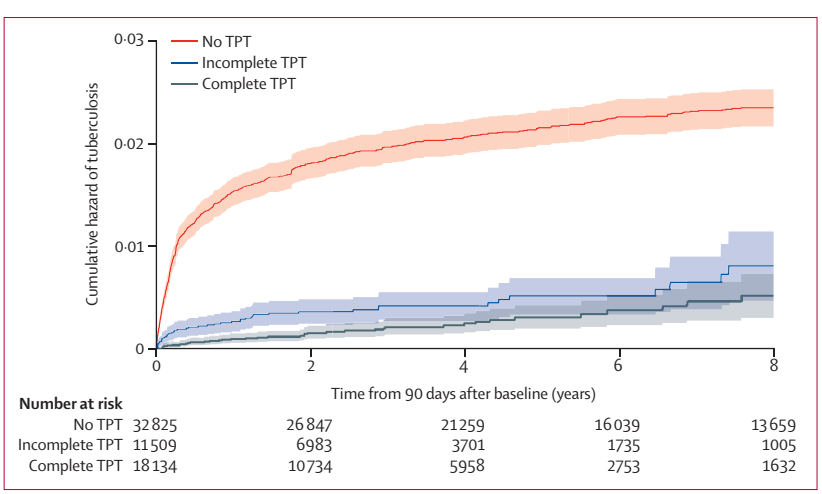


Figure 3: **Cumulative hazard of incident tuberculosis by TPT completion status over follow-up time in low-burden and medium-burden settings**

Shaded regions represent 95% CIs. Adjusted hazard ratios comparing these groups are presented in the appendix (p 16). Results include studies from medium-burden settings (20–100 average annual tuberculosis cases diagnosed per 100 000 population) and low-burden settings (<20 average annual tuberculosis cases diagnosed per 100 000 population) only. TPT completion data from high-burden settings (>100 average annual tuberculosis cases diagnosed per 100 000 population) were insufficient to include in this analysis. Follow-up time was limited to 8 years after baseline to align with the available data from medium-burden settings. TPT=tuberculosis preventive treatment.

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suggested slightly lower hazards with 4R than isoniazid, but estimates were imprecise and overlapping (appendix p 17). At 8 years after baseline, the adjusted HRs were 0·51 (95% CI 0·34–0·76) among participants who took an isoniazid regimen and 0·39 (0·14–1·11) among those who took 4R.

We include additional results and discussion of the alternative analytical methods (including models over full follow-up time, over increasing cumulative increments of time, and over discrete time intervals) in the appendix (pp 20 22–25).

Discussion

In this individual-participant-data meta-analysis of more than 84 000 close contacts with a positive tuberculin skin or interferon gamma release assay test from 44 cohort studies in 24 countries, TPT led to a substantial and sustained reduction in tuberculosis risk for at least 8 years in medium-burden settings and at least 13 years in low-burden settings. In high-burden settings, TPT was highly protective initially, but the effect waned within about a year. In medium-burden and low-burden settings, TPT completers showed greater protection in the first year than non-completers, but long-term tuberculosis risk did not differ statistically by completion status. In medium-burden and low-burden settings (which had substantial median follow-up time), we found that most tuberculosis occurred within the first 2 years, supporting existing evidence of this as a crucial period after *M tuberculosis* infection.[24] These findings suggest that scaling up TPT in high-risk groups in settings with tuberculosis incidence of less than 100 per 100 000 population is likely to have a sustained effect, whereas in high-burden settings TPT should be combined with additional interventions to deliver long-term benefit.

These results provide the most comprehensive empirical evidence to date on the duration of the protection achieved by a single course of TPT across epidemiological settings. Our finding of a sustained tuberculosis risk reduction in medium-burden (8 years) and low-burden (13 years) settings is consistent with smaller studies from Brazil (a medium-burden setting) that reported benefit lasting 7–12 years.[15,16] By contrast, in high-burden settings, the initial protective effect eroded within 1–3 years, mirroring trials in people with HIV and South African gold miners, where protection diminished rapidly after treatment completion.[11–14] However, limited follow-up prevented assessment beyond 3 years in high-burden settings in this study. A 2025 observational study in people with HIV in India reported protection up to 6 years, underscoring that important heterogeneity probably exists within the broad category of high-burden settings regarding transmission intensity, background immunity, comorbidities, and health system factors that shape TPT effectiveness and long-term impact.[25]

Our analyses cannot fully disentangle the mechanisms underlying the observed waning of protective effects, particularly in high-burden settings. Our findings support the notion that ongoing transmission and reinfection are likely to be major drivers, consistent with previous evidence.[26,27] Other possible explanations include incomplete sterilisation of existing *M tuberculosis* infection and non-completion of TPT. At 90 days, when most participants who took TPT were still on or just completing their regimen, we observed a smaller protective effect in high-burden settings. Although this finding might indicate reduced sterilisation, we could not assess TPT completion in high-burden settings to investigate its potential contribution. Diagnostic delays and other clinical differences—eg, rates of unrecognised early or subclinical tuberculosis—across settings could also contribute. In medium-burden and low-burden settings, completing TPT conferred the strongest absolute protection, but even partial TPT was associated with significant, long-term tuberculosis risk reduction. Additional information regarding TPT completion in high-burden settings would help to clarify these effects.

These findings have important clinical and policy implications. In medium-burden and low-burden settings, our results suggest that a single course of TPT for high-risk groups might yield sustained reductions in tuberculosis risk and contribute meaningfully to reducing long-term incidence. In high-burden settings, TPT alone is unlikely to provide protection beyond 1–2 years due to the high likelihood of reinfection and possibly reduced sterilisation. Trials of extended or repeated TPT have shown mixed results. A trial in Botswana found greater protection with 36 months versus 6 months of isoniazid, although the effect again waned after completion, further supporting the role of *M tuberculosis* reinfection in driving the observed waning.[11] In South Africa, continuous isoniazid over 6 years was not superior to shorter regimens, and the WHIP3TB trial found no benefit of repeated TPT.[28,29] Pairing TPT with interventions that reduce ongoing *M tuberculosis* transmission—such as improved case finding and infection prevention and control, and addressing structural factors (eg, overcrowding and undernutrition)[30–32]—might be crucial to extend its effective duration. When and how these interventions can best complement TPT (eg, during or after TPT is completed) remain open questions.

There are several notable nuances in interpreting our results. Follow-up duration varied across studies, with progressively fewer studies contributing data at later timepoints. However, results in medium-burden and low-burden settings were consistent when restricted to studies with at least 8 years of follow-up. Time-interaction models reflect relative-scale effects; although HRs approached the null over long-term follow-up in low-burden settings, few late cases occurred and the cumulative hazards indicated sustained absolute protection.

This study has limitations. Most participants who took TPT received 6 months or 9 months of isoniazid,

limiting assessment of regimen heterogeneity. In low-burden settings, 4R seemed to be slightly more protective than isoniazid; however, these estimates were imprecise. Because studies used regimens of differing lengths, early follow-up periods include both participants on treatment and those who had completed it (particularly in low-burden settings), potentially biasing early estimates towards the null in comparison to a population in which people were all actively taking TPT during that time.

We restricted analyses to individuals who tested positive for *M tuberculosis* infection by tuberculin skin or interferon gamma release assay tests at baseline to reduce confounding by indication. However, unmeasured demographic and clinical variables might lead to residual confounding. For example, we were unable to control for other clinical factors or immune-suppressing conditions beyond HIV status, including undernutrition and use of antiretroviral therapy for HIV, or characteristics of the exposure, including bacillary burden of index cases and exposure intensity. Excluding the first 90 days reduced misclassification of prevalent tuberculosis but might omit rapidly progressing cases, particularly in children and immunocompromised individuals. Tuberculosis burden was classified at the country level, which might not reflect subnational variation, possibly leading to some misclassification by burden status or residual confounding in our models. Although we were able to assess the effect of TPT non-completion, we did not have detailed adherence data (eg, percentage of doses taken) and data in the high-burden settings to further parse these results. Additionally, studies conducted in high-burden settings had shorter follow-up time, preventing assessment beyond 3 years. Finally, there was heterogeneity in the protocols and methods of studies comprising our consortium. Although we included random effects for studies and study designs to address this in modelling, our results represent averages across disparate settings within our burden categories. Local dynamics are likely to influence long-term protection of TPT.[33]

In conclusion, in close contacts with evidence of *M tuberculosis* infection, we showed that TPT significantly reduced tuberculosis risk initially and that this effect persisted for at least 8 years in medium-burden settings and 13 years in low-burden settings. TPT completion conferred the greatest early benefit, but TPT non-completers also showed significant, lasting protection. In high-burden settings, we found that the initial protection gained from TPT eroded within about 1 year, highlighting the importance of pairing TPT with interventions that reduce transmission to achieve sustained impact.

Contributors

LRL and LM conceived the study. MPF, JG, and CRH were advisers to this study. LM conducted the initial systematic search, screened and identified studies, and made final decisions regarding study inclusion. LRL, JIC, and LM conducted the updated systematic search, screened and identified studies, and made final decisions regarding study inclusion. JIC, LM, and LRL received and checked data; LM and JIC accessed and verified the underlying data. LRL and LM designed the analyses; LRL conducted all primary analyses and created tables and figures. LRL wrote the first draft of the report. LRL and LM edited subsequent versions of the manuscript until dissemination to the broader author group. LRL, JIC, and LM had access to each individual dataset included. All authors read and edited the drafted manuscript for important intellectual content and assisted in data interpretation. All authors approved the final version of the manuscript. All authors contributed data to the large, merged individual-participant dataset, but some of the data were not accessible to all authors due to data sharing agreements and restrictions by each study group. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

JIC was supported by the US National Institutes of Health (NIH; grant K23AI186597). CRH is on the Data Safety Monitoring Board for the SUDOCU, ACT5, and Decision trials, is Chair of the Trial Steering Committee for UNITE4TB, and was a member of the Board of Directors of the International Union Against Tuberculosis and Lung Disease from 2019 to 2025. IA was supported by the UK National Institute for Health and Care Research (NIHR). MCB was supported by the US NIH (grants U01 AI057786 and U19 AI076217). FA was supported by the Brunei Darussalam Ministry of Health (Brunei Centre for Disease Control). DB-B had grant funding from bioMérieux Colombia, unrelated to the current manuscript. TFB was supported by the Canadian Institutes of Health Research. RKG was supported by grant funding from the UK NIHR, the Royal Society, and the Wellcome Trust, unrelated to the current manuscript. NM was supported by US NIH funding, is a board member of Wits Health Consortium, and has a leadership role at the Setshaba Research Centre. VM was supported by funding from the US NIH, unrelated to the current manuscript. SN has received honoraria from the Karolinska Institutet and Gothia Kompetens, and has indirect shares in AstraZeneca. YS was supported by funding from the US NIH (grants R35GM146612, R01AI170116, and 75N93019C00052), unrelated to the current manuscript. CS was supported by the US NIH (grants N01-AI95383 and N01-AI70022). JAV is a federal employee with the US National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) at the Centers for Disease Control and Prevention (CDC). This work was not funded or sponsored by CDC, and the data, results, and opinions included in this manuscript do not reflect the views of positions of this federal agency or the US Government. JG was supported by funding from the US NIH, unrelated to the current manuscript. All other authors declare no competing interests.

Data sharing

The data used for this analysis can be made available upon reasonable request to the corresponding author once all relevant substudies from the consortium are reported and completed. The data dictionary can be made available upon request to the corresponding author. We welcome proposals to collaborate on projects using these data.

Acknowledgments

We acknowledge and thank the participants and investigators in each of these studies.

Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

References

1 Salazar-Austin N, Dowdy DW, Chaisson RE, Golub JE. Seventy years of tuberculosis prevention: efficacy, effectiveness, toxicity, durability, and duration. *Am J Epidemiol* 2019; **188:** 2078–85.

2 Chihota V, Gombe M, Gupta A, et al. Tuberculosis preventive treatment in high TB-burden settings: a state-of-the-art review. *Drugs* 2025; **85:** 127–47.

3 WHO. Implementing the end TB strategy: the essentials, 2022 update. Dec 16, 2022. https://www.who.int/publications/i/item/9789240065093 (accessed July 28, 2025).

4 WHO. Global tuberculosis report 2025. Nov 12, 2025. https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/tb-reports/global-tuberculosis-report-2025 (accessed Aug 24, 2026).

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See **Online** for appendix

5 UN General Assembly. Political Declaration of the High-Level Meeting on the Fight Against Tuberculosis: resolution adopted by the General Assembly. Oct 16, 2023. https://digitallibrary.un.org/record/4025280?ln=en&v=pdf (accessed Sept 18, 2025).

6 Vasiliu A, Martinez L, Gupta RK, et al. Tuberculosis prevention: current strategies and future directions. *Clin Microbiol Infect* 2024; **30:** 1123–30.

7 Smieja M, Marchetti C, Cook DJ, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. *Cochrane Database Syst Rev* 2000; **1999:** CD001363.

8 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.

9 Hamada Y, Ford N, Schenkel K, Getahun H. Three-month weekly rifapentine plus isoniazid for tuberculosis preventive treatment: a systematic review. *Int J Tuberc Lung Dis* 2018; **22:** 1422–28.

10 Martinez L, Seddon JA, Horsburgh CR, et al. Effectiveness of preventive treatment among different age groups and *Mycobacterium tuberculosis* infection status: a systematic review and individual-participant data meta-analysis of contact tracing studies. *Lancet Respir Med* 2024; **12:** 633–41.

11 Samandari T, Agizew TB, Nyirenda S, et al. Tuberculosis incidence after 36 months' isoniazid prophylaxis in HIV-infected adults in Botswana: a posttrial observational analysis. *AIDS* 2015; **29:** 351–59.

12 Churchyard GJ, Fielding KL, Lewis JJ, et al. A trial of mass isoniazid preventive therapy for tuberculosis control. *N Engl J Med* 2014; **370:** 301–10.

13 Johnson JL, Okwera A, Hom DL, et al. Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. *AIDS* 2001; **15:** 2137–47.

14 Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet* 2014; **384:** 682–90.

15 Golub JE, Cohn S, Saraceni V, et al. Long-term protection from isoniazid preventive therapy for tuberculosis in HIV-infected patients in a medium-burden tuberculosis setting: the TB/HIV in Rio (THRio) study. *Clin Infect Dis* 2015; **60:** 639–45.

16 Teixeira LAA, Santos B, Correia MG, et al. Long-term protective effect of tuberculosis preventive therapy in a medium/high tuberculosis incidence setting. *Clin Infect Dis* 2024; **78:** 1321–27.

17 WHO. WHO operational handbook on tuberculosis Module 1: prevention—tuberculosis preventive treatment, second edition. Sept 9, 2024. https://www.who.int/publications/i/item/9789240097773 (accessed Oct 21, 2025).

18 Martinez L, Cords O, Horsburgh CR, Andrews JR, Pediatric TB Contact Studies Consortium. The risk of tuberculosis in children after close exposure: a systematic review and individual-participant meta-analysis. *Lancet* 2020; **395:** 973–84.

19 Martinez L, Campbell JI, Linde L, et al. The effectiveness of isoniazid preventive treatment among contacts of multidrug-resistant tuberculosis: a systematic review and individual-participant meta-analysis. *Am J Respir Crit Care Med* 2026; **212:** 129–37.

20 Wells G, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed Oct 20, 2025).

21 Velen K, Shingde RV, Ho J, Fox GJ. The effectiveness of contact investigation among contacts of tuberculosis patients: a systematic review and meta-analysis. *Eur Respir J* 2021; **58:** 2100266.

22 Hernán MA. The hazards of hazard ratios. *Epidemiology* 2010; **21:** 13–15.

23 Stensrud MJ, Hernán MA. Why use methods that require proportional hazards? *Am J Epidemiol* 2025; **194:** 1504–06.

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

25 Agarwal R, Nyendak M, Chava N, et al. Long-term protection from tuberculosis preventive treatment among people with human immunodeficiency virus in a high-burden tuberculosis setting: an observational cohort study from India. *Clin Infect Dis* 2025; **81:** 970–79.

26 Vega V, Rodríguez S, Van der Stuyft P, Seas C, Otero, L. Recurrent tuberculosis: a systematic review and meta-analysis of the incidence rates and the proportions of relapse and reinfection. *Thorax* 2021; **76:** 494–502.

27 da Costa FBP, Nicol MP, Botha M, et al. *Mycobacterium tuberculosis* infection and tuberculosis disease in the first decade of life: a South African birth cohort study. *Lancet Child Adolesc Health* 2024; **8:** 891–99.

28 Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med* 2011; **365:** 11–20.

29 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.

30 Bhargava A, Bhargava M, Meher A, et al. Nutritional supplementation to prevent tuberculosis incidence in household contacts of patients with pulmonary tuberculosis in India (RATIONS): a field-based, open-label, cluster-randomised, controlled trial. *Lancet* 2023; **402:** 627–40.

31 Jesus GS, Gestal PFPS, Silva AF, et al. Effects of conditional cash transfers on tuberculosis incidence and mortality according to race, ethnicity and socioeconomic factors in the 100 Million Brazilian Cohort. *Nat Med* 2025; **31:** 653–62.

32 Saunders MJ, McQuaid CF, Sinha P, Martinez L, Seddon JA, Dodd PJ. Global, regional, and national estimates of tuberculosis incidence averted by eliminating undernutrition in adults: a modelling study. *Lancet Glob Health* 2026; **14:** 103935.

33 Theron G, Jenkins HE, Cobelens F, et al. Data for action: collection and use of local data to end tuberculosis. *Lancet* 2015; **386:** 2324–33.