The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis

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Summary

Background **WHO estimates that a third of the world's population has latent tuberculosis infection and that less than 5% of those infected are diagnosed and treated to prevent tuberculosis. We aimed to systematically review studies that report the steps from initial tuberculosis screening through to treatment for latent tuberculosis infection, which we call the latent tuberculosis cascade of care. We specifically aimed to assess the number of people lost at each stage of the cascade.**

Methods **We did a systematic review and meta-analysis of study-level observational data. We searched MEDLINE (via OVID), Embase, and Health Star for observational studies, published between 1946 and April 12, 2015, that reported primary data for diagnosis and treatment of latent tuberculosis infection. We did meta-analyses using random and fixed effects analyses to identify percentages of patients with latent tuberculosis infection completing each step in the cascade. We also estimated pooled proportions in subgroups stratified by different characteristics of interest to assess risk factors for losses.**

Results **We identified 58 studies, describing 70 distinct cohorts and 748 572 people. Steps in the cascade associated with greater losses included completion of testing (71·9% [95% CI 71·8–72·0] of people intended for screening), completion of medical evaluation (43·7% [42·5–44·9]), recommendation for treatment (35·0% [33·8–36·4]), and completion of treatment if started (18·8% [16·3–19·7]). Steps with fewer losses included receiving test results, referral for evaluation if test positive, and accepting to start therapy if recommended. Factors associated with fewer losses were immune-compromising medical indications, being part of contact investigations, and use of rifamycin-based regimens.**

Interpretation **We identify major losses at several steps in the cascade of care for latent tuberculosis infection. Improvements in management of latent tuberculosis will need programmatic approaches to address the losses at each step in the cascade.**

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Introduction

In many high-income countries, reactivation of latent tuberculosis infection is estimated to account for more than 80% of all incident cases of tuberculosis, and prevalence of latent tuberculosis might exceed 50% in certain populations.[1] There is no gold-standard test to diagnose latent tuberculosis, but based on currently available immune-based tests, a third of the world's population has presumptive latent tuberculosis.[2,3] Although an updated estimate of the global burden of latent tuberculosis would be very helpful,[4] it is accepted that there is a vast reservoir of latent infection, from which it is estimated that 100 million people will develop active, contagious tuberculosis over their lifetimes.[5]

Management of latent tuberculosis is considered to be one of the core interventions for tuberculosis elimination. In the 1960s and 1970s, several studies showed that isoniazid for 6–12 months could significantly reduce the risk of reactivation of active tuberculosis in people with a positive tuberculin skin test (TST).[6,7] However, the length of therapy, need for close follow-up, and risk of potentially fatal hepatotoxicity[8] reduced uptake, acceptance, and completion of therapy.[9] These problems substantially reduce the cost-effectiveness[10] and the population-level epidemiological impact of this approach.[11,12] As a result, in the past two decades, randomised trials have aimed to identify shorter regimens that are as effective as, yet safer and more acceptable, than isoniazid.[13] These trials have identified several alternative rifamycin-based regimens that have recently been recommended for treatment of latent tuberculosis infection.[14–16]

Factors associated with non-completion of treatment of latent tuberculosis have received considerable attention: a recent systematic review identified 68 studies investigating non-completion from North American centres alone. The authors noted the importance of strategies to improve treatment adherence that are specific to the context and populations being served, and that a one-size-fits-all approach was unlikely to be successful.[12] However, there has been very little recognition for the impact of losses during the many steps in patients' trajectories before therapy is begun. People with latent tuberculosis might not be identified for screening, and even if they are, might not be tested, or a TST might be done but not

Research in context

Evidence before this study

Latent tuberculosis infection is estimated to affect more than a third of the world's population. Although methods exist to diagnose and effectively treat latent tuberculosis infection, they are slow and imprecise. This scarcity leads to difficulties in the identification and treatment of this vast pool of infected people, which has been identified as a key barrier to global tuberculosis control. There are multiple steps in the care process from initial identification of people with latent tuberculosis infection who could potentially benefit from therapy, until treatment completion. Patients can, and do, drop-out or are lost at each of these steps. We searched three electronic databases, for studies that were published between 1948 and June 20, 2016, describing the full procedures of diagnosis, evaluation and treatment of latent tuberculosis. There have been multiple studies of the problems leading to non-completion of therapy once it has been started: one systematic review identified 68 studies from North America alone. This systematic review showed inconsistent associations between adherence and patient factors or treatment characteristics. Far fewer studies have estimated the losses and drop-outs at earlier steps, largely because these patients are not seen by health-care personnel, and so it is unknown how often and why these problems occur. We undertook this systematic review to understand the extent, and reasons for patient losses, during the entire latent tuberculosis cascade of care.

Added value of this study

To our knowledge, our study is the first to conceptualise the latent tuberculosis cascade of care, and develop an explicit framework of analysis to account for the losses during each individual step in this cascade, from initial identification of risk of infection, through to completion of treatment. We show estimated losses at each step, and identify the patient and health system factors associated with those losses. Notably, losses before starting therapy accounted for greater net reduction of the public health benefit of latent tuberculosis infection management than did patient non-adherence with therapy once started.

Implications of all the available evidence

Interventions that aim to reduce losses at the early steps of the latent tuberculosis cascade of care should enhance the public health impact of diagnosis and treatment of infection more than will interventions that focus on improving patients' completion of treatment. To achieve the goals of the new WHO End TB Strategy of reducing the tuberculosis incidence rate to less than ten infections per 100 000 by 2035, latent tuberculosis management needs to be substantially scaled up. Our findings suggest that every step in the entire cascade of latent tuberculosis care will need improvement to achieve that goal. And, although we clearly demonstrated the extent of the problem and some health-system factors associated, very little published evidence was found of successful interventions to reduce the losses at every step.

read, or an interferon-gamma release assay (IGRA) result might not be received by providers. Individuals with a positive TST or IGRA might not complete medical evaluation (eg, symptom check, physical exam, and chest radiography),[17–21] and providers might not recommend therapy or treatment might not be started or completed. Given the lack of recognition of this problem, it is not surprising there have been very few studies of interventions to prevent the losses and drop-outs at these steps. With the new End TB Strategy to eliminate tuberculosis by 2035, there has been increased recognition of the importance of addressing latent tuberculosis infection. This systematic review offers evidence for the importance of addressing the losses along the cascade of care, if efforts to eliminate tuberculosis are going to be successful.

We aimed to systematically review the published research about the so-called cascade of care in latent tuberculosis diagnosis and treatment. Specific outcomes of interest included: the number of people eligible for testing for latent tuberculosis infection; the number who initiated and completed screening with IGRA or TST; and the number with positive tests who had chest radiographic and medical evaluation; and who were prescribed, started, and, completed treatment for latent tuberculosis infection.

Methods

Search strategy and selection criteria

We did a systematic review and meta-analysis of study-level observational data. We searched MEDLINE (via OVID), Embase, and Health Star for cohort reports of diagnosis and treatment of latent tuberculosis infection published between 1946 and April 12, 2015. To identify additional relevant articles, we searched the Cochrane Database of Systematic Reviews and used reference lists of identified reviews from this search, original articles, other recent reviews, and recent treatment guidelines.[22] Search terms were "latent TB OR latent tuberc* OR tuberc* infection or inactive tuber*" OR "screening OR contact OR investigation OR finding OR tuberc* screening" OR "adherence OR completion OR compliance OR yield".

We used MOOSE guidelines for reporting of observational studies.[23] We included studies published in English, French, Italian, or Spanish that reported primary data. We excluded randomised trials, case-control studies, reviews, editorials, and letters, in addition to surveillance or other studies that reported aggregate data and not outcomes at the level of individuals. We included studies that reported, at minimum, the number of people intended for latent tuberculosis infection screening and the number completing latent tuberculosis infection

treatment (ie, the two ends of the cascade). Studies that reported contact investigations without reporting the number intended to be screened were included if the number of index cases with pulmonary tuberculosis was given. In these studies, we extrapolated the number of contacts from the number of index cases, using the average number of close contacts identified per index case reported in two recent systematic reviews.[7,24] We included studies that did not report the number of patients completing therapy for latent tuberculosis infection if the number starting therapy was given. In this circumstance, we extrapolated the number completing therapy based on the number starting and indication for testing, using data from a recent systematic review on treatment completion that was stratified by indication.[12]

Two reviewers (HA and DM) independently reviewed titles, then abstracts, and then full-text articles. At each step, decisions were compared and disagreements about study selection resolved by consensus between the two reviewers.

Data analysis

Data were abstracted by two reviewers (HA and DM) using a standardised data abstraction form. Both authors in duplicate extracted data for 14 studies and then findings were checked for concordance. Data from the remaining studies were abstracted by a single reviewer. Data collected included author, years, country (using World Bank classifications as low-income or middle-income country [LMIC] or high income), population screened and risks for latent tuberculosis infection, type of screening test (TST or IGRA), characteristics of population studied (age, sex, etc), and treatment given (isoniazid or rifamycin based). Programmes were labelled outbreaks or pilots if characterised as such by the authors of the source paper; otherwise they were considered routine. Numbers extracted were the reported numbers of patients who: were intended to be screened (1), tested (2), TST read or IGRA result obtained (3), completed medical evaluation (4), recommended therapy (5), accepted or started therapy (6), and completed therapy (7). Data for risk factors for losses at these steps were also recorded.

The pooled proportion of participants with latent tuberculosis infection completing each step in the cascade was estimated using random effects meta-analyses with PROC Nlmixed in SAS version 9.3. These pooled proportions were also estimated in subgroups stratified by different characteristics of interest. The key outcome was the proportion who completed therapy for latent tuberculosis infection of all those estimated to have latent tuberculosis in the population being screened. This was calculated by dividing the number of people who completed therapy by those estimated to have latent tuberculosis (total number intended to be screened multiplied by the proportion with a positive test), and was used to generate forest plots of the estimated impact on the full range of the cascade. Extrapolated values for number intended to screen and completing therapy were not used for the analysis of factors associated with losses at each step. To estimate the cumulative losses at each step, the proportion remaining at that step was multiplied by the proportion remaining after the preceding step; we estimated these pooled proportions and 95% CI using fixed meta-analyses (using PROC

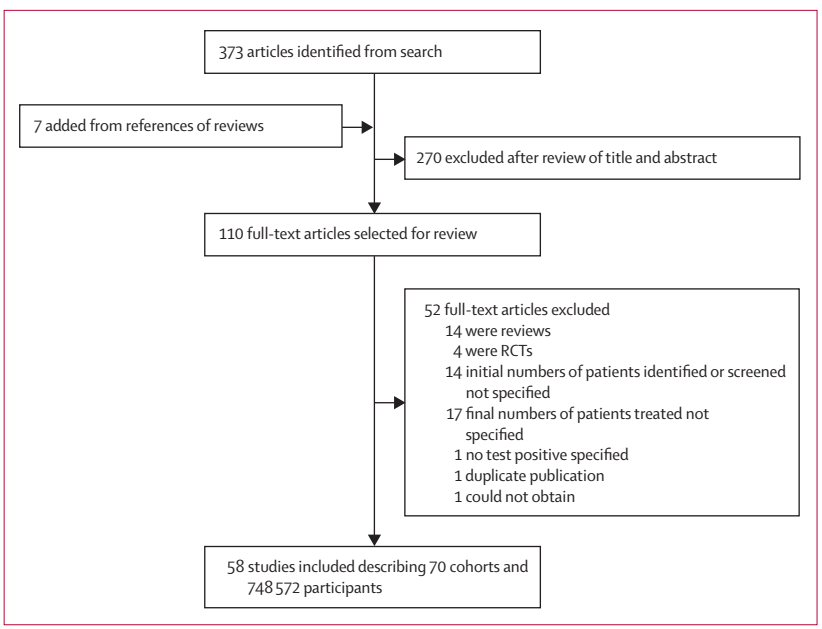

Figure 1: **Study selection**
RCT=randomised controlled trials.

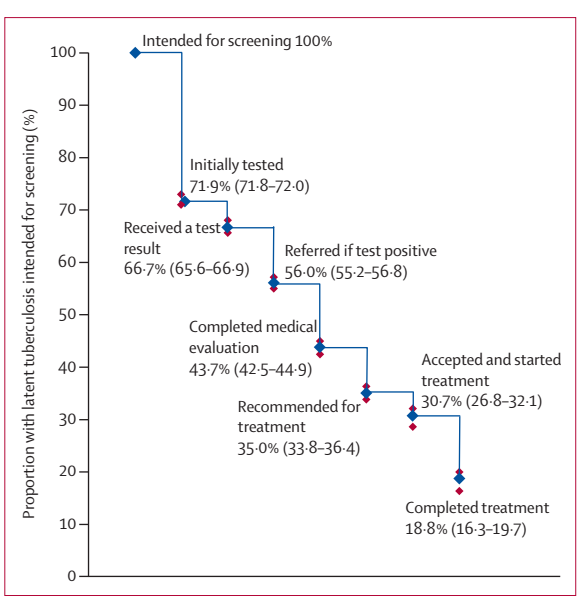

Figure 2: **Losses and drop-outs at each stage of the cascade of care in latent tuberculosis**
Numbers in parentheses are 95% CIs. The value for each level is calculated as the product of the value from the preceding step, multiplied by the pooled estimate for that step (from fixed-effects analysis).

Glimmix in SAS version 9.3). We estimated heterogeneity with the I^2 statistic.[25] Sensitivity analyses were done by repeating analyses without key groups for which services might be organised very differently: prison populations, HIV-infected populations, and the general population.

See Online for appendix

Role of the funding source

The funder had no role in study design, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

We identified 110 full-text articles for review, of which 58 studies were considered eligible and included in the systematic review (figure 1).[10,17–21,26–77] All studies were published after 1990, and 50 were published since 2000. These studies described 70 distinct study populations (henceforth referred to as cohorts; n=748 572), of which 59 (n=741 540) were from high-income countries and 11 (n=7032) from LMICs (studies summarised in appendix pp 2–3). 36 cohorts (n=418 367) received care as part of routine programmes, whereas 25 (n=327 533) received pilot interventions and nine (n=2672) were part of outbreak investigations (appendix p 4). TST was the method of testing in 60 cohorts (n=731 032), whereas six (n=16 059) were tested with IGRA (two used IGRA only if TST was positive) and four (n=1481) did not have details reported for which test was used.

The most important losses in the cascade occurred at four steps: initial testing of those intended for screening, completing medical evaluation if test was positive, provider recommendation of treatment, and completing therapy if started (figure 2).

The most important predictive factor for completion of the first step of screening was the indication (table 1). Of people estimated to have latent tuberculosis infection, 86% with immune-compromising medical indication (eg, patients with HIV or diabetes mellitus or those being treated with tumour-necrosis factor antagonists) completed screening and received a result, as did 83% of marginalised groups (eg, homeless people) and 79% of people who had been in contact with someone with tuberculosis for more than 5 h per week (ie, contacts), compared with 62% of those from the general population samples and 43% of migrants (table 1). The proportion completing this step in the cascade, as well as all subsequent steps, was highly heterogeneous, with I^2 values exceeding 95% for most strata. Of those who had a TST, 94% returned for reading, and 98% of those tested with IGRA had valid results (appendix p 5).

The pooled prevalence of positive tests for latent tuberculosis infection was 61% for populations in LMICs versus 25% for populations in high-income countries (appendix p 6). The intermediate steps from positive test to starting therapy were reported in fewer cohorts: referral for evaluation (18 cohorts), completing medical evaluation (29 cohorts), treatment recommended (26 cohorts), and therapy accepted (25 cohorts; appendix pp 7–10). Over 90% of participants with latent tuberculosis infection who received positive tests were referred for further evaluation, medical evaluation was completed by 89% of those referred, providers recommended treatment to 70%, and 90% started if they were recommended treatment (appendix pp 7–10).

The cumulative results of these steps are summarised in table 2. Treatment acceptance and initiation of isoniazid therapy was lower than for that of rifamycin-containing regimens (62% *vs* 83% of people with positive tests). Higher proportions of people with medical indications (85%) and contacts (75%) started treatment, as compared with marginalised groups (56%), migrants (55%), or the general population (51%; table 2). Of people

	Number of cohorts	Screened/eligible (n/N)*	Pooled event rate (95% CI)†	I^2
Country income level				
High	57	513 880/728 442	75·6% (67–84)	100·0%
Low or middle	8	3666/6295	51·3% (19–83)	99·8%
Services				
Routine	33	298 207/405 143	66·9% (53–81)	100·0%
Outbreak investigation	9	2245/2672	88·0% (75–100)	96·7%
Pilot intervention	23	217 094/326 922	74·1% (60–89)	100·0%
Study populations				
Medical	5	2619/3363	86·1% (68–100)	96·0%
Contacts	27	151 911/180 420	79·3% (69–90)	99·9%
Marginalised	11	206 406/277 763	83·3% (69–98)	100·0%
Migrants	12	15 062/54 011	43·4% (20–67)	100·0%
General population	10	141 548/219 180	62·1% (37–87)	100·0%
Age				
Adults only	37	236 047/358 323	66·9% (54–80)	99·5%
Children only	9	58 448/68 934	60·4% (33–88)	99·8%
All ages (or not reported)	19	223 051/307 480	86·4% (77–96)	100·0%
Testing for latent tuberculosis‡				
TST alone	57	507 781/717 436	75·1% (66–84)	100·0%
IGRA with or without TST	6	8998/16 059	62·3% (28–97)	99·9%
Not specified	2	767/1242	39·4% (0–100)	99·8%
Treatment for latent tuberculosis				
Isoniazid	42	301 609/399 086	71·5% (60–83)	100·0%
Rifamycin containing (with or without isoniazid)	12	138 805/212 759	80·3% (64–97)	99·9%
Moxifloxacin and ethambutol	1	139/232	59·9% (0–100)	..
Not specified	10	76 993/122 660	71·5% (48–95)	100·0%
Years of data collection				
Up to 2000	25	362 480/461 814	79·0% (67–91)	98·0%
After 2000	40	155 066/272 923	69·0% (56–81)	99·0%

TST=tuberculin skin test. IGRA=interferon-gamma release assay. *Numerator is participants who successfully completed screening (ie, results available; if number not reported, data are for those initially tested; N=517 546); denominator is participants who were eligible for screening (N=734 737). †Pooled estimates and 95% CIs for participants with latent tuberculosis infection who completing screening from random effects meta-analysis. ‡TST read or valid IGRA results obtained by provider.

Table 1: **Characteristics associated with completed screening**

who started therapy, only 62% completed overall (appendix p 11); in LMICs only 52% of those who started completed treatment compared with 70% in high-income countries.

As a result of all the losses in the cascade, of all people estimated to have latent tuberculosis infection, only 50% of people with medical indications completed latent tuberculosis infection treatment, compared with 14% of migrants, and 10% of the general population cohorts (table 3). This estimate of overall impact was very heterogeneous, with wide variation in different settings and populations (appendix pp 13–14). In three sensitivity analyses, exclusion of HIV-infected populations (three cohorts), prison populations (six cohorts, including one very large study), and the general population (ten cohorts) resulted in findings very similar to the results with all cohorts (appendix p 12).

Reasons for not completing screening were put into two main categories: social situations impeding the completion of screening and health-system issues (panel). Barriers to the referral and recommendation of treatment included: being considered too old (older than 35 years), low health-provider knowledge about the benefits and risks of therapy for latent tuberculosis infection, and social situations. Barriers to treatment completion included side-effects to drugs, health-systems issues and social situations (panel).

On June 20, 2016, we repeated our search using the same search strategy and inclusion criteria to check whether any additional papers had been published since our analysis. Two additional articles would have met our study inclusion criteria. In one study,[78] 43 (29%) of 149 refugees arriving in Philadelphia (PA, USA) with "non-communicable tuberculosis conditions" completed latent tuberculosis infection therapy, and in the other study,[79] 35% of all close contacts with latent tuberculosis infection in the USA in 2012 completed treatment. Although the completion rate was higher than the pooled estimates in our findings, both studies identified drop-outs and losses at each stage of the cascade, similar to the major findings of this Article.

	Number of cohorts	Started treatment/ eligible (n/N)*	Pooled event rate (95% CI)†	I^2
Country income level				
High	57	56 514/90 798	64·6% (56–74)	99·1%
Low or middle	6	1023/1351	72·2% (48–96)	95·1%
Services				
Routine	33	32 735/53 519	62·7% (51–75)	99·5%
Outbreak investigation	8	368/465	80·9% (63–99)	99·7%
Pilot intervention	22	24 434/38 165	63·9% (49–78)	88·4%
Study populations				
Medical	4	720/851	84·8% (67–100)	80·1%
Contacts	25	26 258/38 667	74·8% (64–85)	99·3%
Marginalised	11	22 464/36 363	56·4% (35–77)	90·3%
Migrants	13	2005/3998	54·6% (36–73)	0·0%
General population	10	6090/12 270	50·8% (29–73)	99·9%
Age				
Adults only	36	28 154/45 766	62·6% (51–74)	100·0%
Children only	8	22 013/35 622	69·1% (47–91)	99·9%
All ages (or not reported)	19	7370/10 761	68·9% (54–84)	99·9%
Testing for latent tuberculosis				
TST alone	57	56 712/90 610	64·2% (55–73)	99·2%
IGRA with or without TST	6	825/1539	75·3% (53–98)	0%
Not specified	0	..	..	..
Treatment for latent tuberculosis				
Isoniazid	41	31 987/53 498	62·3% (52–72)	99·4%
Rifamycin containing (with or without isoniazid)	12	13 021/20 200	83·3% (72–94)	0%
Moxifloxacin and ethambutol	1	104/119	87·7% (58–100)	..
Not specified	9	12 425/18 332	43·1% (20–66)	90%
Years of data collection				
Up to 2000	26	42 265/67 728	58·0% (44–72)	89·0%
After 2000	37	15 272/24 421	70·0% (60–80)	99·0%

TST=tuberculin skin test. IGRA=interferon-gamma release assay. *Numerator is participants who successfully started treatment (if number missing, data were for participants recommended to start; N=57 537); denominator is participants who were eligible for treatment (ie, those who tested positive; N=92 149). †Pooled estimates and 95% CIs for participants with latent tuberculosis infection who started treatment from random-effects meta-analysis.

Table 2: **Characteristics associated with starting treatment**

Discussion

Findings from our systematic review and meta-analysis show that important losses occurred at the steps of initial screening, completing medical evaluation, and starting and completing therapy in in all settings and study populations for latent tuberculosis infection.

We used the HIV cascade of care as a model. First recognised in 2009 to quantify the importance and cumulative impact of losses at each stage of care,[80,81] this framework identified five points along the continuum of care where HIV patients are commonly lost to follow-up. These pretreatment losses accounted for much greater reduction in effective HIV care than non-adherence to antiretroviral therapy.[26,50,80] Applying this care framework to latent tuberculosis infection could help to identify problems and develop strategies to improve diagnosis, management, and treatment completion.[80] By focusing on better patient retention and referral, particularly in high-risk groups, a substantial portion of patients with latent tuberculosis will be kept in care, initiated on appropriate regimens, and ultimately complete treatment, thereby reducing the reservoir of latent tuberculosis from which active tuberculosis develops.[82]

Although some steps of the cascade were associated with major losses, other steps were consistently done much better. Of those tested with TST, about 94% received their results. Additionally, more than 90% of patients with positive tests were referred for further evaluation, and of those who were recommended therapy, more than 90% agreed to start. The negative findings

	Number of cohorts	Completed treatment/eligible (n/N)*	Pooled event rate (95% CI)†	I^2
Country income level				
High Income	59	35 062/134 329	23·4% (16–30)	99·9%
Low or middle income	11	889/3603	16·7% (4–29)	99·3%
Services				
Routine	36	21 670/71 782	21·2% (13–29)	99·7%
Outbreak investigation	9	330/627	45·5% (20–71)	98·2%
Pilot intervention	25	13 951/65 523	18·0% (9–27)	99·9%
Study populations				
Medical	5	479/1176	50·4% (20–81)	99·7%
Contacts	31	17 914/48 320	29·3% (19–40)	99·8%
Marginalised	11	12 603/48 844	21·0% (7–35)	99·2%
Migrants	13	1608/20 104	14·3% (5–24)	92·8%
General population	10	3347/19 488	9·7% (2–17)	99·8%
Age				
Adults only	37	16 609/77 491	18·3% (11–26)	99·8%
Children only	12	4735/14 749	18·3% (6–31)	99·8%
All ages (or not reported)	21	14 607/45 692	33·5% (19–48)	99·7%
Testing for latent tuberculosis				
TST alone	60	35 028/134 184	21·1% (15–28)	99·9%
IGRA with or without TST	6	629/2959	35·1% (8–63)	99·4%
Not specified	4	294/789	21·6% (0–47)	98·1%
Treatment for latent tuberculosis				
Isoniazid	47	20 089/75 438	18·5% (12–25)	99·8%
Rifamycin containing (with or without isoniazid)	12	7790/27 672	49·6% (30–69)	99·5%
Moxifloxacin and ethambutol	1	93/199	46·7% (0–100)	..
Not specified	10	7979/27 672	14·0% (3–25)	99·9%
Years of data collection				
Up to 2000	27	25 935/88 287	18·0% (10–27)	99·9%
After 2000	43	9754/49 645	24·0% (16–33)	99·3%

TST=tuberculin skin test. IGRA=interferon-gamma release assay. *Numerator is participants who successfully completed prescribed treatment once started (if number not reported, data are for those who were recommended treatment by the provider; N=35 951); denominator is participants who started treatment (N=137 932). †Pooled estimates and 95% CIs for participants with latent tuberculosis infection who completed treatment are from random-effects meta-analysis.

***Table* 3: Characteristics associated with completing treatment**

suggest important areas for improvement, whereas the positive findings suggest where training and motivation appear to have been successful. We speculate that the fewer overall losses in high-risk populations, such as close contacts[48,57] or patients with serious medical disorders,[49] might be due to their high-risk status, as a result of which they may have received more intensive health care. This finding suggests that better outcomes might be seen in other groups of patients if they receive a similar intensity of care.[18,50,63,83]

There has been a major investment in the past two decades to complete more than a dozen major trials of shorter courses of therapy for latent tuberculosis infection with rifamycin-containing regimens.[8,55] Our findings show that these shorter regimens were associated with a 20% greater treatment completion. However, in a hypothetical cohort of 1000 people with latent tuberculosis infection, improving the proportion screened from 70% to 90%, the proportion evaluated from 79% to 90%, and the proportion starting treatment from 74% to 90%, but keeping isoniazid as the therapy regimen (assumed 61% treatment completion) would result in 445 completing effective latent tuberculosis infection therapy. On the other hand, without changing the losses at the earlier steps, only 336 would complete effective therapy if a rifamycin-containing regimen was introduced (completion 82%). Therefore treatment losses earlier on can result in greater overall reduction in public health benefit of latent tuberculosis infection management.

The primary focus of other reviews of latent tuberculosis infection management have been the prevalence of latent tuberculosis in contact investigations[7] or adherence to treatment once started.[12,24] To our knowledge, this is the first systematic review to evaluate the full cascade of care for latent tuberculosis infection through all steps of the diagnostic and treatment process. We included 46 studies that reported on factors affecting the losses at each step, allowing tabulation of potentially actionable items to improve the cascade. Although screening and treatment for latent tuberculosis infection might be more difficult in high-burden countries due to the financial constraints and need to prioritise limited resources for detection and treatment of active tuberculosis cases, WHO recommends latent tuberculosis treatment[16] only for the highest risk groups in LMICs. These high-risk groups include people living with HIV and children younger than 5 years old who are household contacts of newly diagnosed active tuberculosis cases. Our findings highlight the need to carefully evaluate the public health impact of this approach, given the potential reduction in the benefits due to losses and drop-outs at different steps in the cascade.

This systematic review and meta-analysis has several limitations. Most papers included did not completely report on the different steps in the cascade; only ten publications reported on all steps. Only 18 studies reported data on referrals, medical evaluation, and recommendations to start treatment, and all of these were from high-income countries, thus limiting the generalisability of findings related to these steps. The type of test used was missing in four cohorts, and treatment regimen was not reported by ten studies, somewhat limiting analysis of these factors. Heterogeneity was high for most analyses, even within many of the stratified analyses, suggesting substantial unexplained variation in the results. Our study, similar to other meta-analyses of observational studies was subject to potential selection bias, as well as differences in individual study measurements.[23,24] The relatively large numbers of studies allowed a number of stratified analyses to help to address heterogeneity, which might have helped limit these problems. Finally, only 11 cohorts from LMICs were included in this review, compared

***Panel:* Risk factors and reasons associated with losses at different steps of the cascade, identified in the studies included in the Article**

Initial identification
- Health authorities unable to contact (invalid addresses)[51]
- Immigration examination is reason for consult (fear of not being allowed entry into the country based on tuberculosis status)[26]

Testing of intended for screening
- Health-care workers hired before pre-employment TST mandated[42]
- Not offered TST by health-care worker or physician due to:
  - medical contraindications (ie, previous treatment for latent or active tuberculosis, skin conditions, or recent measles injection)[17,19,26,27,29,31,50]
  - language barriers[27]
- No interest in being tested[28]
- Self-perceived low risk of tuberculosis infection (had not been in contact with tuberculosis in the past)[26]

Completing screening and testing
- Did not perceive tuberculosis to be a serious disease[26]
- Health systems issues:
  - hard to access the clinic or long wait times[17,28,29]
  - does not like needles (for the interferon-gamma release assay)[28]
  - stigma, mistrust, or unwillingness to visit tuberculosis centre[18,28]
  - difficulties with health insurance[30,31]
  - end of local health awareness campaigns[29]
- Social situations impeding screening completion:
  - language or cultural barriers[26,27]
  - feels too ill[28]
- No administrative enforcement of mandated post-exposure testing[42]

Referral for medical evaluation
- Older age (35 years of age or older)[17,32–34]
- Low perceived risk of tuberculosis infection[19,73]
- Less parental supervision for attending tuberculosis clinic appointments (eg, high-school students)[69]
- Termination of financial compensation[31]

Recommending treatment
- Low health-care worker knowledge about the need for therapy for latent tuberculosis infection[35,36,37,38,39,40,41,42,71]
- Medically contraindicated (ie, previous treatment for latent or active tuberculosis or elevation of liver enzymes)[17,20,26,32,68]
- Social situations impeding treatment:
  - substance abuse[17,20,28,72]
  - recent release from jail or prison[43,45,47]
  - no transportation[40,44]
  - fear of deportation or immigration status[30,46]

Starting treatment
- Refusal to start due to immigrant status[35,53,58]
- Older age (35 years of age or older)[63]
- Low perceived risk of active tuberculosis (for themselves or their children)[10 19,20,28,38,51,58,60]
- Poor linkages between the tuberculosis programme and general health services (ie, delays between TST and clinic visit)[44,58]
- Not receiving a chest radiograph[65]
- Previous latent tuberculosis treatment in their country of origin[69]
- HIV infection[65]

Completing treatment
- Development of adverse effects after medication (ie, hepatotoxicity, neurological, psychiatric, or gastrointestinal symptoms)[17,20,21,28,32,34,40,43,48–56]
- Long duration of treatment course[42]
- Health systems issues:
  - mistrust of the health-care system[28]
  - patient did not know when to come back for treatment refills[37]
  - physicians did not consider adherence to therapy to be part of their responsibility[17]
- Treated elsewhere[10,17,20]
- Social situations impeding treatment completion:
  - relocation or moving[30,32,33,43,54,55,60]
  - leaving jail or prison[34,47,59]
  - immigrant status[30,58,53,62]
  - substance abuse[28,30,43,45,61]

TST=tuberculin skin test.

with 59 cohorts from high-income countries, and only three cohorts reported data from HIV-positive subpopulations. Since the largest global burden of latent tuberculosis infection occurs in LMICs, and many of these countries have high HIV coinfection rates, there is a need for more information regarding the cascade of care in these high-burden settings and high-risk populations.

We believe that our findings provide important insights to inform the ongoing global efforts to enhance the programmatic management of latent tuberculosis infection. Improving the cascade of care for latent tuberculosis infection will require systematic investigation of the extent and risk factors of the losses at each step, including trials to identify cost-effective and feasible interventions that can be adopted by tuberculosis control programmes. In resource-limited settings, the diagnosis and adequate treatment of all people with active tuberculosis must remain the priority. However, to maximise the public health impact of expanded diagnosis

and treatment, programmes must plan strategies to correct the problems identified in the cascade of care for latent tuberculosis infection.

Contributors

HA and DM conceived of the study and did the literature review, data collection, and data analysis for the paper. All authors evaluated the data. All authors reviewed the draft, had critical input, and reviewed the final submission.

Declaration of interests

We declare no competing interests.

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