A scoping review of paediatric latent tuberculosis infection care cascades: initial steps are lacking

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ABSTRACT
Background and objectives Identifying and treating children with latent tuberculosis infection (TB infection) is critical to prevent progression to TB disease and to eliminate TB globally. Diagnosis and treatment of TB infection requires completion of a sequence of steps, collectively termed the TB infection care cascade. There has been no systematic attempt to comprehensively summarise literature on the paediatric TB infection care cascade.

Methods We performed a scoping review of the paediatric TB infection care cascade. We systematically searched PubMed, Cumulative Index to Nursing and Allied Health Literature, Cochrane and Embase databases. We reviewed articles and meeting abstracts that included children and adolescents ≤21 years old who were screened for or diagnosed with TB infection, and which described completion of at least one step of the cascade. We synthesised studies to identify facilitators and barriers to retention, interventions to mitigate attrition and knowledge gaps.

Results We identified 146 studies examining steps in the paediatric TB infection care cascade; 31 included children living in lower-income and middle-income countries. Most literature described the final cascade step (treatment initiation to completion). Studies identified an array of patient and caregiver-related factors associated with completion of cascade steps. Few health systems factors were evaluated as potential predictors of completion, and few interventions to improve retention were specifically tested.

Conclusions We identified strengths and gaps in the literature describing the paediatric TB infection care cascade. Future research should examine cascade steps upstream of treatment initiation and focus on identification and testing of at-risk paediatric patients. Additionally, future studies should focus on modifiable health systems factors associated with attrition and may benefit from use of behavioural theory and implementation science methods to improve retention.

BACKGROUND
The WHO has named identification and treatment of tuberculosis (TB) infection a cornerstone of efforts to eliminate TB by 2030.1 (note: in this article, we will use the term ‘TB infection’ to distinguish patients with latent TB infection from those with TB disease.) The United Nations has set shorter term milestones to end the TB epidemic, including provision of TB preventive treatment (TPT) for 30 million people exposed to infectious TB and/or diagnosed with TB infection between 2018 and 2022, of whom 6.3 million received treatment in 2018–2019.2 TB infection diagnosis and treatment require completion of sequential steps, which together constitute the TB infection care cascade.3–11

What do the new findings imply?
Future research should focus on early steps of the paediatric TB infection care cascade and should seek to identify and address modifiable health systems barriers to retention in the cascade.

Key questions
What is already known?
► Most patients at risk for latent tuberculosis infection (TB infection) do not complete the steps needed to diagnosis and treat TB infection (the ‘TB infection care cascade’).
► Children face unique barriers to completion of the TB infection care cascade.

What are the new findings?
► Although many studies have evaluated portions of the paediatric TB infection care cascade, they have primarily focused on the final step of the cascade: treatment initiation to treatment completion.
► Little published research has described sustainable interventions that target modifiable barriers to completing upstream steps of the paediatric TB infection care cascade.

What do the new findings imply?
► Future research should focus on early steps of the paediatric TB infection care cascade and should seek to identify and address modifiable health systems barriers to retention in the cascade.
The full TB infection cascade is not always needed—existing guidance recommends that child contacts <5 years old and people living with HIV exposed to infectious TB can be started on TPT following a clinical exam without preceding TB infection testing.22 A focused systematic review of contact case management of child contacts of individuals with infectious TB in high burden countries identified health system (eg, lack of protocols and lack of healthcare worker (HCW) education), structural (eg, cost of transport) and patient/family level barriers to completing evaluation for TB and initiation/completion of TPT.23 Because of heterogeneity in TB screening guidelines between countries, and because testing is not always needed for contact case management in high burden countries, that review did not examine gaps in TB infection diagnosis in detail. However, even in high TB burden settings, strengthening testing pathways will help to avoid unnecessary TPT, improve acceptability of treatment and expand treatment beyond close contacts.24

We performed a scoping review of paediatric TB infection care cascade literature with a goal of understanding facilitators and barriers to care for children evaluated and treated for TB infection. We sought to understand the cascade in both high and low resource areas and in the full range of clinical care and research settings. We defined seven steps of the care cascade, based on the cascade outlined by Alsdurf and colleagues: (1) intention to test to receipt of the test (tuberculin skin test (TST) or interferon gamma release assay (IGRA)), (2) receipt of test to test read, (3) test read to referral for medical evaluation, (4) referral for medical evaluation to completion of medical evaluation, (5) completion of medical evaluation to treatment recommendation, (6) treatment recommendation to treatment start and (7) treatment start to treatment completion (figure 1).3 25

Our study complements the prior review of the contact case management approach used in many LMIC23 by including studies from low-burden settings and focusing in detail on diagnostic steps of the cascade.

METHODS
Scoping review questions
The questions we sought to answer in this scoping review were:

1. What are barriers and facilitators of paediatric TB infection care cascade completion in high-income and low-income and middle-income (LMIC) countries?
2. What strategies have been employed to improve retention in the paediatric TB infection care cascade?
3. What key knowledge gaps remain in literature about the paediatric TB infection care cascade?

Population, concept and context
We included articles and meeting abstracts that specifically described: (1) children or adolescents; (2) patients screened for or diagnosed with TB infection; and (3) completion of at least one step of the care cascade.

The population of interest in this review was paediatric patients tested for and diagnosed with TB infection. We defined paediatric patients as patients age 0–21 years old; we further defined ‘children’ as patients aged 0–11 years old and ‘adolescents’ as 12–21 years old. We focused on patients tested for TB infection (ie, who had undergone a TB infection test using a TST or IGRA). However, to retain a broad view of TB infection diagnosis and treatment in high-burden settings, we included studies that reported on child contacts <5 years old receiving TPT following exposure to infectious TB who had not received a TB infection test, when those children were grouped with paediatric patients diagnosed with TB infection (ie, who had a positive TB infection test).

The key concepts in this review were facilitators and barriers to completion of one or more cascade steps and interventions designed to improve retention. Reporting of a specific step of the cascade was defined as reporting the number of patients that started and completed the step. Assignment of steps in the cascade was based on data as reported in each study. When ambiguous, proper assignment was determined by our interpretation of the reported data. We defined barriers and facilitators as factors that were statistically associated with completion of one or more cascade steps or that authors causally linked to completion of a step. For example, adverse medication effects that caused patients to discontinue TPT, as reported by study authors, were considered barriers to cascade completion, even if no statistical test was done. For facilitators and barriers that were statistically associated with completion, we focused on factors that were significant in multivariable analyses and that were specifically found to affect paediatric patients. We defined interventions as programmes.
strategies or activities designed to prevent loss from one or more step of the care cascade. Because our goal was to understand the range of interventions targeting cascade retention, we included descriptions of interventions even when efficacy was not evaluated within a study.

The context of this review was all clinical and geographic settings in which TB infection care was provided. Articles and abstracts were excluded if they were not written in English, Spanish, French or German.

Search strategy
We systematically searched PubMed, Embase, CINAHL and Cochrane for terms related to the TB infection care cascade in children and adolescents, including terms pertinent to latent TB infection, children and adolescents, and specific steps of the care cascade (full search strategy in online supplemental appendix 1). The initial database searches were performed on 10 February 2020 and updated on 13 November 2020. We did not restrict the timeframe of publications.

Data extraction
We collected all references using EndNote V.7.7 and imported them into Covidence. We screened titles and abstracts for eligibility and obtained full texts of articles and abstracts meeting criteria. Using a standardised data sheet, one reviewer (JIC) extracted publication year, country, number of children and adolescents included, inclusion of children <5 years old, population, care cascade steps reported, number of patients completing specified care cascade steps, reasons for non-completion of steps, factors statistically associated with step completion, interventions used to improve retention, behavioural theories used for intervention design and treatment used. Studies that reported multiple steps of the care cascade were included in the synthesis of each relevant step. Data were tabulated, summarised and categorised to identify themes and gaps in the literature.

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews to guide data reporting.26 Because of heterogeneity in study type, objectives and use of interventions, we did not perform formal quality assessments, an approach commonly used in scoping reviews.27 Patients and public were not involved in the design or conduct of this study.

RESULTS
We identified 146 studies examining steps in the TB infection care cascade for children and adolescents, including 143 primary analyses and 3 systematic reviews (figure 2 and table 1). Of included studies, 51 included children and adolescents living in LMIC (table 2). Twenty-one studies reported comparative effectiveness of interventions to promote retention in at least one cascade step.

Table 3 summarises barriers, facilitators, interventions tested and knowledge gaps.

Eight studies included in this review reported on paediatric patients living with HIV.28–35 Of these, HIV seroprevalence was high (23.5%) in one study, which reported on children and adolescents starting TPT in Brazil.30 In the remainder, HIV seroprevalence was relatively low (0.8%–4.5%). Facilitators and barriers to cascade completion in children and adolescents with HIV were not analysed separately in any included study.

The complete care cascade
We identified seven studies that documented completion of all seven cascade steps.28 36–41 These studies described the cascade within specific scenarios: school-based screenings,39 40 screening among asylum seekers 37 and contact investigations.28 36 38 41 42 The proportion of paediatric patients who completed or appropriately exited the care cascade ranged from 65% in a large study of US high school students39 to 100% in a small Australian contact tracing study.41 Only one study, which described contact tracing in Uganda, was conducted in a resource-limited setting.28 We identified a single study that used the overarching care cascade framework to design interventions for retention. This cluster-randomised trial of health centres in five countries (Canada, Benin, Ghana, Indonesia and Vietnam), named ACT4, used locally developed interventions to address specific identified barriers to retention.42 Effective strategies reported to date from this trial—from Ghana—included provision of financial support to patients, education from HCWs, home visits and decreased wait times at clinics.43
Table 1  Summary of included studies

| Reference                  | Year | N     | Country       | Study type                             | Population                                      | Steps reported | Factors statistically associated with completion in children/adolescents | Factors descriptively associated with completion in children/adolescents |
|----------------------------|------|-------|---------------|----------------------------------------|------------------------------------------------|---------------|------------------------------------------------------------------------|-----------------------------------------------------------------------|
| Studies conducted in low-income and middle-income countries |      |       |               |                                        |                                                |               |                                                                        |                                                                        |
| Alavi and Sefidgaran       | 2008 | 5000  | Iran          | Prospective cross-sectional            | Child and adolescent students undergoing scheduled screening | 1,2           | –                                                                      | (-) Patient/caregiver refusal (-) Children refused testing (-) Concurrent infectious diseases |
| Albanese et al             | 2015 | 228   | Brazil        | Retrospective cohort                   | Children* and adolescents exposed to individuals with infectious TB | 5–7           | –                                                                      | –                                                                      |
| Baliashvili et al          | 2018 | 739   | Georgia       | Prospective cohort/contact investigation | Children* and adolescents exposed to individuals with infectious TB | 1             | (-) Age 5–14 years (vs 0–4 years)                                      | –                                                                      |
| Bamrah et al               | 2014 | 43    | Federated States of Micronesia | Prospective cohort/contact investigation | Children* and adolescents exposed to individuals with infectious MDR-TB | 7             | –                                                                      | (-) Medication adverse effects (-) Concurrent infectious diseases |
| Barss et al                | 2020 | 225   | Ghana         | Prospective cohort                     | Children* exposed to individuals with infectious TB | 1,5,6         | –                                                                      | (+) Multimodal solutions targeting knowledge, stigma and cost associated with diagnosis and treatment |
| Bedoya and Arbeláez Montoya | 2014 | 70    | Colombia      | Prospective cross-sectional/contact investigation | Children* exposed to individuals with infectious TB | 1,7           | (-) Male sex (+) Insured                                              | –                                                                      |
| Bonnet et al               | 2017 | 339   | Uganda        | Prospective cohort                     | Children* exposed to individuals with infectious TB | 1–7           | –                                                                      | –                                                                      |
| Chakhaia et al             | 2014 | 83    | Georgia       | Prospective cohort/contact investigation | Children* exposed to individuals with infectious TB | 7             | –                                                                      | –                                                                      |
| Coprada et al              | 2016 | 1227  | Philippines   | Retrospective cross-sectional/contact investigation | Children* exposed to individuals with infectious TB | 1,6           | –                                                                      | (-) Transferred care (-) Only presumptive cases referred for testing (-) Children in school (-) Caregivers too busy to bring children to DOTS facility (-) Transportation costs (-) Inconsistent supply of TST and medication (-) Problems with communication between clinic and caregivers (-) Limited time to conduct home visits for contacts that did not follow-up |
| Reference | Year | N  | Country                  | Study type                  | Population                                      | Steps reported | Factors statistically associated with completion in children/adolescents | Factors descriptively associated with completion in children/adolescents |
|-----------|------|----|--------------------------|-----------------------------|--------------------------------------------------|----------------|------------------------------------------------------------------------|------------------------------------------------------------------------|
| Diallo et al<sup>63</sup> | 2018 | 829 | Australia, Benin, Brazil, Canada, Ghana, Guinea and Indonesia | RCT                          | Children* and adolescents receiving TB infection | 5–7            | (+) Treatment with 4R (vs 9H)                                          | (-) Patient/caregiver refusal (-) Pregnancy                            |
| Do Nascimento and Sant'Anna<sup>162</sup> | 2016 | 158 | Brazil                     | Retrospective cohort          | Children* and adolescents receiving TB infection treatment | 7              | -                                                                      | -                                                                      |
| Dorjee et al<sup>102</sup> | 2019 | 5234 | India                      | Prospective cohort            | Child and adolescent students undergoing scheduled screening | 5–7           | -                                                                      | (-) Concurrent infectious diseases (-) Medication adverse effects (-) Patient/caregiver refusal |
| Gomes et al<sup>39</sup> | 2011 | 2631 | Guinea-Bissau              | Prospective cohort            | Children* and adolescents exposed to individuals with infectious TB | 1,6,7         | (+) Age >5 years (vs age ≤5 ears)                                      | (-) Moved out of catchment (-) Travelling (-) Forgot (-) Not receiving medication |
| Hamdi et al<sup>112</sup> | 2016 | 87  | Tunisia                    | Retrospective cohort          | Children* and adolescents exposed to individuals with infectious TB | 7              | (+) Near relationship with index case (+) Close contact with index case | -                                                                      |
| Hosten et al<sup>51</sup> | 2018 | 210 | Jordan                     | Retrospective cohort/contact investigation | Child* and adolescent refugees children exposed to individuals with infectious TB | 1,2,6         | -                                                                      | (-) Supply shortages                                                   |
| Huang et al<sup>66</sup> | 2018 | 4724 | China                      | Prospective cross-sectional/contact investigation | Adolescent students exposed to individuals with infectious TB | 1,5           | (-) Lower parental education (-) Concern about medication adverse effects (-) Negative opinion provided by outside clinician (-) Perceived discrimination/stigma | -                                                                      |
| Huerga et al<sup>49</sup> | 2019 | 198 | Armenia                    | Prospective cohort/contact investigation | Children* and adolescents exposed to individuals with infectious MDR-TB | 1              | -                                                                      | (-) Caregiver refusal (-) Moved out of catchment (-) Transferred care (-) Unable to reach family |
| Ilievska-Poposka et al<sup>103</sup> | 2018 | 61  | North Macedonia           | Retrospective cohort          | Children* and adolescents receiving TB infection treatment | 7              | -                                                                      | -                                                                      |
| Reference | Year | N  | Country | Study type         | Population                                                                 | Steps reported | Factors statistically associated with completion in children/adolescents | Factors descriptively associated with completion in children/adolescents |
|-----------|------|----|---------|-------------------|----------------------------------------------------------------------------|----------------|------------------------------------------------------------------------|---------------------------------------------------------------------|
| Khalid et al | 2020 | 3226 | Sudan   | Prospective cross-sectional | Child and adolescent students undergoing scheduled screening               | 1              | –                                                                      | (-) Absenteeism (-) Chronic disease (-) Unwillingness to participate |
| Li et al   | 2018 | 560 | China   | Qualitative/survey    | Adolescent students exposed to individuals with infectious TB               | 6              | Associated with perceived ability to adhere (+) Knowledge of TB transmission (+) Knowledge of TB treatment and policy | Associated with perceived ability to adhere (+) Concern about spreading TB to others (+) Contact with cases (+) Desire to follow physician's advice (+) Desire to prevent active TB therapy/ability to adhere (-) Concerns about cost (-) Concerns about duration of therapy/stress of taking (-) Concerns about medication adverse effects (-) Perceived low risk |
| Li et al   | 2016 | 42  | China   | Qualitative/survey    | Children and adolescents with TB infection; caregivers; healthcare workers | 1              | –                                                                      | (Associated with perceived ability to adhere) (-) Concerns about medication adverse effects (-) Lack of patient/caregiver knowledge about testing and treatment (-) Clinician concerns about cost (-) Clinician concerns about duration of therapy (-) Clinician concerns about therapy effectiveness (-) Workloads and lack of clinician incentives |
| Machado et al | 2009 | 47  | Brazil  | Prospective cohort    | Children* and adolescents exposed to individuals with infectious TB         | 7              | –                                                                      | –                                                                   |
| Mendonca et al | 2016 | 286 | Brazil  | Retrospective cohort  | Children* and adolescents receiving TB infection treatment                 | 7              | (+) Place of residence – Human Development Index score (-) Contact with adult TB contacts not receiving TB treatment | (-) Contact with adult TB contacts not receiving TB treatment |

Table 1 Continued
| Reference          | Year | N      | Country   | Study type                      | Population                                           | Steps reported | Factors statistically associated with completion in children/adolescents | Factors descriptively associated with completion in children/adolescents |
|--------------------|------|--------|-----------|---------------------------------|------------------------------------------------------|---------------|------------------------------------------------------------------------|------------------------------------------------------------------------|
| Said et al         | 2019 | 398    | Tanzania  | Prospective cohort              | Children* exposed to individuals with infectious TB  | 1,5,6         | –                                                                      | (−) Caregiver refusal                                                 |
| Silva et al        | 2016 | 1078   | Brazil    | Prospective cohort/contact investigation | Children* and adolescents tested for TB                | 2,3,5–7       | (+) Knowledge about BCG vaccination preventive effects (−) Knowledge about TB transmission (−) Higher cost of transportation to clinic (−) Lower income |
| Soussi et al       | 2013 | 25     | Tunisia   | Retrospective cohort/contact investigation | Children* exposed to individuals with infectious TB  | 1,6           | –                                                                      | –                                                                      |
| van Zyl et al      | 2006 | 335    | South Africa | Retrospective cohort/contact investigation | Children* exposed to individuals with infectious TB  | 6,7           | (+) Treatment with 3HR (vs 6H) (−) Treatment supervised by community supporter or clinic healthcare worker (vs by caregiver) |
| Villarino et al    | 2015 | 905    | USA, Brazil, Canada, China and Spain | RCT | Children* and adolescents receiving TB infection treatment | 7             | (+) Treatment with 3HP (vs 9H) (−) Medication adverse effects (−) Patient/caregiver refusal (−) Physician decision to discontinue treatment |
| Wang et al         | 2017 | 1330.041 | China    | Retrospective cohort            | Adolescent students undergoing scheduled screening   | 1,5–7         | –                                                                      | –                                                                      |
| Wong and Lee       | 2020 | 439    | Malaysia  | Prospective cross-sectional      | Child* and adolescent students undergoing scheduled screening | 1–4          | –                                                                      | –                                                                      |
| Wysocki et al      | 2016 | 68     | Brazil    | Retrospective cross-sectional/contact investigation | Children and adolescents exposed to individuals with infectious TB | 1,7          | –                                                                      | –                                                                      |
| Studies conducted in high-income countries                     |      |        |           |                                 |                                                       |               |                                                                        |                                                                        |
| Adams et al        | 2014 | –      | –         | Systematic review of systematic reviews | Children* and adolescents initiating TPT           | 7             | –                                                                      | –                                                                      |

Continued
| Reference          | Year | N   | Country     | Study type                      | Population                                                                 | Steps reported | Factors statistically associated with completion in children/adolescents | Factors descriptively associated with completion in children/adolescents |
|--------------------|------|-----|-------------|--------------------------------|-----------------------------------------------------------------------------|---------------|-----------------------------------------------------------------------|----------------------------------------------------------------------|
| Adler-Shohet et al | 2014 | 118 | USA         | Retrospective cohort           | Child students exposed to individuals with infectious MDR-TB                  | 1–7           | –                                                                     | (−) Medication adverse effects (−) Patient/caregiver refusal         |
| Ahmad et al        | 2020 | 224 | Denmark     | Retrospective cohort           | Children and adolescents seeking asylum                                     | 1–7           | –                                                                     | (−) Patient/caregiver refusal (−) Fear of blood draws                |
| Ahn et al          | 2015 | 108 | South Korea | Prospective cohort/contact investigation | Neonates exposed to an HCW with infectious TB                              | 1–7           | –                                                                     | (−) Patient/caregiver refusal to continue therapy (−) Medical instability/elevated liver enzymes |
| Al Mekaini et al   | 2014 | 669 | United Arab Emirates | Prospective cross-sectional | Children and adolescents receiving outpatient primary care                  | 1,2           | (+) Siblings participating in the study (−) Age<10 years (vs≥10 years) | (−) Patient/caregiver refusal                                      |
| Aldeco et al       | 2011 | 103 | Slovenia     | Prospective cohort/contact investigation | Neonates exposed to an HCW with infectious TB                              | 1,2           | –                                                                     | –                                                                    |
| Anaraki et al      | 2018 | 291 | UK          | Prospective cohort/contact investigation | Adolescent students exposed to individuals with infectious TB                | 1             | –                                                                     | –                                                                    |
| Assefa et al       | 2018 | –   | –           | Systematic review              | Children and adolescents receiving TB infection treatment                   | 7             | (+) Treatment with 3RH (vs 6H) (−) Treatment with 4RH (vs 9H)         | –                                                                    |
| Bennet and Eriksson| 2017 | 349 | Sweden      | Retrospective cohort           | Child and adolescent immigrants                                              | 4             | –                                                                     | (−) Moved out of catchment (−) Patient/caregiver refusal (−) Deemed to be ‘psychologically unfit’ for treatment |
| Bennet et al       | 2014 | 546 | USA         | Retrospective cohort           | Adolescent refugees                                                         | 6,7           | –                                                                     | (−) Inability to contact by mail (−) Patient/caregiver refusal (−) Adverse medication effects |
| Berlioz et al      | 2008 | 1813| France      | Prospective cohort/contact investigation | Children receiving outpatient primary care                                   | 1–6           | –                                                                     | (−) Age <12 years (vs older ages)                                    |
| Bibi et al         | 2002 | 28016| Israel      | Retrospective cohort           | Adolescent immigrants                                                       | 1–5           | –                                                                     | –                                                                    |
| Bieberly and Al    | 2008 | 47  | USA         | Retrospective cohort           | Children and adolescents receiving TB infection                             | 7             | –                                                                     | (+) Age <12 years (vs older ages)                                    |
| Bishara et al      | 2015 | 220 | Israel      | Retrospective cohort           | Child and adolescent immigrants                                              | 5–7           | (−) Age <5years                                                      | –                                                                    |
| Blumberg et al     | 2005 | 286 | USA         | Prospective cohort             | Adolescents receiving TB infection treatment                                | 7             | –                                                                     | –                                                                    |
### Table 1  Continued

| Reference                  | Year | N    | Country    | Study type                              | Population                                                      | Steps reported | Factors statistically associated with completion in children/adolescents | Factors descriptively associated with completion in children/adolescents |
|----------------------------|------|------|------------|-----------------------------------------|----------------------------------------------------------------|---------------|------------------------------------------------------------------------|------------------------------------------------------------------------|
| Bock et al61                | 1999 | 446  | USA        | Prospective cohort                      | Children* and adolescents undergoing TB screening               | 2             | -                                                                      | -                                                                      |
| Boyd et al25                | 2017 | 88   | Australia  | Retrospective cohort                    | Children* and adolescents diagnosed with TB infection           | 5–7           | -                                                                      | (-) Moved out of catchment                                             |
| Brassard and Lamare61       | 2000 | 456  | Canada     | Prospective cohort/contact investigation | Children* exposed to a physician with infectious TB              | 1,4–7         | (+) Fewer children living in household                                 | (-) Inability to contact by mail                                       |
|                            |      |      |            |                                         |                                                                 |               | (-) Caregiver concerns about treatment                                 | (-) Caregivers’ misunderstanding of duration of treatment             |
|                            |      |      |            |                                         |                                                                 |               | (-) Forgetting                                                         | (-) Forgetting                                                         |
|                            |      |      |            |                                         |                                                                 |               | (-) Lack of cooperation from child                                     | (-) Lack of cooperation from child                                     |
|                            |      |      |            |                                         |                                                                 |               | (-) Concurrent infectious diseases                                      | (-) Concurrent infectious diseases                                      |
| Brassard et al68           | 2006 | 3710 | Canada     | Prospective cohort                      | Child* and adolescent immigrants                                | 1–4,7         | (+) More family members undergoing TB testing                          | (-) Patient/caregiver refusal                                         |
|                            |      |      |            |                                         |                                                                 |               | (-) Older age at time of screening                                     | (-) Moved out of catchment                                             |
|                            |      |      |            |                                         |                                                                 |               | (-) Longer time since immigration                                      |                                                                        |
| Breuss et al96             | 2002 | 34   | Switzerland| Retrospective cohort                   | Children and adolescents seeking asylum                          | 4             | -                                                                      | -                                                                      |
| Bright-Thomas et al108      | 2010 | 334  | UK         | Retrospective cohort                    | Children* and adolescents receiving TB infection treatment      | 7             | -                                                                      | -                                                                      |
| Calder et al107            | 2008 | 491  | New Zealand| Prospective cohort/contact investigation| Children* and adolescents exposed to individuals with infectious TB | 1,5,6         | -                                                                      | (-) Patient/caregiver refusal                                         |
| Calzada-Hernandez et al99  | 2015 | 3    | Spain      | Retrospective cohort                    | Children and adolescents receiving anti-TNFs therapy            | 5–7           | -                                                                      | -                                                                      |
| Cass et al143              | 2005 | 1582 | USA        | Prospective cohort                      | Children* and adolescents receiving TB infection treatment      | 7             | (+) Spanish speaking                                                  | (-) Contact investigation                                             |
|                            |      |      |            |                                         |                                                                 |               | (+) Contact investigation                                              | (+) Incentive programme                                               |
|                            |      |      |            |                                         |                                                                 |               | (-) Clinic location                                                    | (-) Missed appointment calls and letters                              |
|                            |      |      |            |                                         |                                                                 |               | (-) Referred to a public health nurse                                  |                                                                        |

Continued
| Reference       | Year | N     | Country     | Study type                          | Population                                                                 | Steps reported | Factors statistically associated with completion in children/adolescents | Factors descriptively associated with completion in children/adolescents |
|-----------------|------|-------|-------------|-------------------------------------|---------------------------------------------------------------------------|----------------|-----------------------------------------------------------------------|-----------------------------------------------------------------------|
| Catho et al[69] | 2015 | 43    | France      | Retrospective cohort/contact investigation | Children* and adolescents exposed to individuals with infectious MDR-TB     | 7              |                                                                      |                                                                      |
| Chang et al[31] | 2013 | 1525  | USA         | Retrospective cohort                | Children* and adolescents diagnosed with TB infection                      | 7              | (+) Home follow-up (vs clinic follow-up)                               | –                                                                     |
| Chang et al[33] | 2014 | 1872  | USA         | Retrospective cohort                | Children* and adolescents diagnosed with TB infection                      | 4–7            | (-) Older age (-) Non-Hispanic race (-) Adverse medication effects    | (-) Transferred care (-) Patient/caregiver refusal (-) Pregnancy     |
| Cheng et al[71] | 1997 | 627   | USA         | RCT                                 | Children* and adolescents receiving outpatient primary care                | 2              | (+) Education and school form intervention (+) Nurse visit intervention | (-) Lack of time (-) Transportation/money barriers (-) Forgot (-) Family health problems |
| Cheng et al[70] | 1996 | 37    | USA         | Prospective cohort                  | Children* and adolescents screened for TB infection                       | 2              |                                                                      |                                                                      |
| Christy et al[92] | 1996 | 401   | USA         | Prospective cross-sectional         | Children* and adolescents receiving outpatient primary care                | 2              |                                                                      |                                                                      |
| Coly and Morisky[13] | 2004 | 610   | USA         | RCT                                 | Children and adolescents receiving TB infection treatment                  | 7              | (+) Higher score on medication-taking behaviour index (+) Living with both parents | –                                                                     |
| Crossa et al[14] | 2015 | 16,995 | USA         | Retrospective cohort                | Children* and adolescents tested for TB                                    | 7              |                                                                      | –                                                                     |
| Cruz et al[99]  | 2014 | 40    | USA         | Retrospective cohort                | Children* and adolescents receiving TB infection treatment                  | 7              |                                                                      | (-) Medication adverse effects                                        |
| Cruz and Starke[32] | 2013 | 1383  | USA         | Retrospective cohort                | Children* and adolescents receiving TB infection treatment                  | 7              |                                                                      | (-) Medication adverse effects (-) Patient/caregiver refusal         |
| Cruz and Starke[31] | 2014 | 404   | USA         | Retrospective cohort                | Children* and adolescents receiving TB infection treatment                  | 7              | (+) Treatment with 4R (vs 9H)                                          | (-) Medication adverse effects (-) Patient/caregiver refusal         |
| Cruz and Starke[96] | 2012 | 289   | USA         | Retrospective cohort                | Children* and adolescents diagnosed with TB infection                      | 5–7            | (+) DOPT (vs SAT)                                                    | (-) Moved out of catchment (-) Patient/caregiver refusal            |
| Daskalaki et al[33] | 2011 | 58    | USA         | Retrospective cohort                | Children* and adolescents receiving TB infection treatment                  | 7              |                                                                      | (-) Medication adverse effects (-) Pregnancy                         |

Table 1 Continued
| Reference             | Year | N   | Country       | Study type                        | Population                                      | Steps reported | Factors statistically associated with completion in children/adolescents | Factors descriptively associated with completion in children/adolescents |
|-----------------------|------|-----|---------------|-----------------------------------|-------------------------------------------------|---------------|------------------------------------------------------------------------|------------------------------------------------------------------------|
| De Pontual et al[81]  | 2004 | 92  | France        | Retrospective cohort              | Children* and adolescents receiving TB infection treatment | 5,6           | -                                                                      | -                                                                      |
| Dewan et al[82]       | 2006 | 5   | USA           | Prospective cohort/contact investigation | Children* and adolescents exposed to individuals with infectious TB | 5–7           | -                                                                      | -                                                                      |
| Dobler and Marks[119] | 2012 | 51  | Australia     | Retrospective cohort              | Children* and adolescents receiving TB infection treatment | 7             | -                                                                      | -                                                                      |
| Donahue et al[27]     | 2019 | 7   | USA           | Prospective cohort                | Children receiving TB infection treatment        | 7             | -                                                                      | (+) Telem medicine DOPT                                              |
| Elliot et al[86]      | 2018 | 36  | Australia     | Retrospective cohort              | Child* and adolescent refugees                   | 5–7           | -                                                                      | (-) Inability to contact families                                     |
| Erkens et al[71]      | 2014 | 1120| The Netherlands| Retrospective cohort              | Children* and adolescents diagnosed with TB infection | 7             | -                                                                      | (-) Transferred care                                                  |
| Erkens et al[34]      | 2016 | 3301| The Netherlands| Retrospective cohort              | Children* and adolescents diagnosed with TB infection | 7             | -                                                                      | (-) Medication adverse effects                                       |
| Fathoala et al[72]    | 2006 | 130 | UK            | Retrospective cohort              | Children* and adolescents diagnosed with TB infection | 7             | -                                                                      | -                                                                      |
| Feja et al[98]        | 2008 | 51  | USA           | Retrospective cohort              | Children* and adolescents receiving MDR-TB infection treatment | 7             | (+) Care at a government health department clinic (vs non-department of health clinic) | (-) Medication adverse effects                                       |
| Gaensbauer et al[20]  | 2018 | 1174| USA           | Retrospective cohort              | Children* and adolescents receiving TB infection treatment | 7             | (+) Contact with active TB case (+) Speaking language common to >5% of TB infection patients (+) Treatment with 4R (vs 9H) | (-) Medication adverse effect (-) Moved out of catchment (-) Patient/caregiver refusal |
| George et al[84]      | 2011 | 193 | USA           | Prospective cross-sectional       | Children* who were international adoptees        | 4             | -                                                                      | -                                                                      |
| Guix-Comellas et al[29]| 2017 | 213 | Spain         | Retrospective cohort              | Children* and adolescents receiving TB infection treatment | 7             | -                                                                      | -                                                                      |
| Hatzenbuehler et al[38]| 2016 | 925 | USA           | Prospective cohort                | Adolescent students undergoing scheduled screening | 1–7           | -                                                                      | -                                                                      |
Table 1 Continued

| Reference          | Year | N     | Country         | Study type                      | Population                              | Steps reported | Factors statistically associated with completion in children/adolescents | Factors descriptively associated with completion in children/adolescents |
|--------------------|------|-------|-----------------|---------------------------------|------------------------------------------|----------------|------------------------------------------------------------------------|------------------------------------------------------------------------|
| Herchline and Trent | 2018 | ND    | USA             | Retrospective cohort            | Adolescent refugees                      | 7              | –                                                                      | (+) Age 13–17 years                                                   |
| Higuchi et al      | 2008 | 43    | Japan           | Prospective cohort/contact investigation | Child and adolescent students exposed to individuals with infectious TB | 7              | –                                                                      | –                                                                      |
| Hill et al         | 2010 | 285   | USA             | Qualitative/survey              | Adolescents receiving TB infection treatment | 7              | –                                                                      | (-) Caregiver barriers: lack of knowledge, work conflicts, costs of seeing providers, concerns about medication adverse effects (-) Clinician-related barriers: lack of knowledge, resistance to recommendations for monthly visits (-) Limited capacity of local health department to provide TB infection care (-) Patient barriers: lack of knowledge, difficulty completing baseline health checks and medication adverse effects |
| Horsburgh et al    | 2010 | 347   | Canada and USA  | Retrospective cross-sectional    | Children* and adolescents receiving TB infection treatment | 7              | –                                                                      | (-) Patient/caregiver refusal                                        |
| Hovell et al       | 2003 | 286   | USA             | Qualitative/survey              | Adolescents receiving TB infection treatment | 7              | (+) Adherence coaching (+) Bicultural (+) School grades (+) Younger age (-) Risk-taking behaviours | –                                                                      |
| Hovell et al       | 2018 | 263   | USA             | RCT                             | Adolescents receiving TB infection treatment | 7              | (+) Time spent in adherence counselling sessions (+) Family encouragement to take therapy (-) Ran out of medication | –                                                                      |

Continued
| Reference         | Year | N    | Country   | Study type                          | Population                                      | Steps reported | Factors statistically associated with completion in children/adolescents | Factors descriptively associated with completion in children/adolescents |
|-------------------|------|------|-----------|-------------------------------------|------------------------------------------------|---------------|-----------------------------------------------------------------------|-----------------------------------------------------------------------|
| Hovell et al[^2]  | 2003 | 286  | USA       | RCT                                 | Adolescents receiving TB infection treatment    | 7             | (+) Adherence coaching                                                 | -                                                                     |
| Hwang et al[^5]   | 2019 | 269  | South Korea| Retrospective cohort/contact investigation | Children* and adolescents exposed to individuals with infectious TB | 1,7           | -                                                                     | -                                                                     |
| Iroh Tam et al[^7] | 2010 | 13   | Ireland   | Retrospective cohort                | Children* and adolescents diagnosed with TB infection | 7             | -                                                                     | -                                                                     |
| Kaiser et al[^6]  | 2015 | 215  | USA       | Prospective cohort/contact investigation | Adolescent students exposed to individuals with infectious TB | 2,5,6         | -                                                                     | -                                                                     |
| Kim et al[^3]     | 2017 | 947  | South Korea| Retrospective cohort/contact investigation | Adolescent students exposed to individuals with infectious TB | 1,5,6         | -                                                                     | -                                                                     |
| Kohn et al[^5]    | 1996 | 864  | USA       | Prospective cohort                  | Adolescent students undergoing scheduled screening | 4,7           | (+) DOPT (vs SAT)                                                     | (-) Patient/caregiver refusal                                    |
| Kominski et al[^15]| 2007 | 794  | USA       | RCT/cost effectiveness              | Children and adolescents receiving TB infection treatment | 7             | (+) Living with both parents                                           | -                                                                     |
| Kondo and Ito[^26]| 2003 | 273  | Japan     | Prospective cohort/contact investigation | Children* exposed to individuals with infectious TB | 5-7           | -                                                                     | -                                                                     |
| Korneva et al[^97]| 2015 | 80   | Russia    | Retrospective cohort                | Children* and adolescents receiving TB infection treatment | 5-7           | -                                                                     | (-) Caregiver refusal                                              |
| Kwara et al[^21]  | 2008 | 132  | USA       | Retrospective cohort                | Children and adolescents receiving TB infection treatment | 7             | -                                                                     | -                                                                     |
| Lardizabal et al[^22]| 2006 | 348  | USA       | Retrospective cohort                | Children* and adolescents receiving TB infection treatment | 7             | -                                                                     | -                                                                     |
| Levesque et al[^75]| 2004 | ND   | Canada    | Retrospective cohort                | Child and adolescent refugees                   | 1             | -                                                                     | -                                                                     |
| Li et al[^4]      | 2010 | 4119 | USA       | Retrospective cohort                | Children and adolescents receiving TB infection treatment | 7             | (+) Treatment with 6R (vs 9H)                                         | -                                                                     |
| Reference          | Year | N   | Country | Study type                           | Population                                                                 | Steps reported | Factors statistically associated with completion in children/adolescents | Factors descriptively associated with completion in children/adolescents |
|--------------------|------|-----|---------|--------------------------------------|-----------------------------------------------------------------------------|----------------|------------------------------------------------------------------------|------------------------------------------------------------------------|
| Lobato et al[176]  | 2003 | 578 | USA     | Retrospective cohort/contact investigation | Children* and adolescents exposed to individuals with infectious TB         | 6              | –                                                                      | –                                                                      |
| Lobato et al[177]  | 2008 | 298 | USA     | Retrospective cross-sectional          | Children* receiving TB infection treatment                             | 7              | –                                                                      | –                                                                      |
| Loutet et al[62]   | 2018 | 44  | UK      | Retrospective cohort                  | Child and adolescent immigrants                                          | 1              | –                                                                      | –                                                                      |
| Macaraig et al[72] | 2018 | 85  | USA     | Retrospective cohort                  | Children and adolescents receiving TB infection treatment                 | 7              | –                                                                      | –                                                                      |
| Martinez-Roig et al[78] | 2003 | 73  | Spain   | Retrospective cohort                  | Children* and adolescents diagnosed with TB infection or exposed to individuals with infectious TB | 7              | –                                                                      | –                                                                      |
| Milinkovic et al[5] | 2018 | 93  | Canada  | Retrospective cohort                  | Children and adolescents diagnosed with TB infection                      | 6,7            | –                                                                      | –                                                                      |
| Minodier et al[70] | 2010 | 4375| Canada  | Prospective cohort                    | Child and adolescent students undergoing scheduled screening              | 1–7            | (+) Location of origin                                                | (-) Patient/caregiver refusal                                      |
|                    |      |     |         |                                      |                                                                             |                | (-) Delay between TST and first clinic visit                           | (-) Transferred care                                               |
|                    |      |     |         |                                      |                                                                             |                | (-) Household composition (living with parents plus grandparents; living with non-child relatives) |                                         |
|                    |      |     |         |                                      |                                                                             |                | (-) Age >16 years (vs younger)                                        |                                         |
| Morisky et al[116] | 2001 | 767 | USA     | RCT                                  | Children and adolescent receiving TB infection treatment                  | 7              | (+) Age <15 years (vs ≥15 years)                                       | –                                                                      |
|                    |      |     |         |                                      |                                                                             |                | (+) Asian ethnicity                                                   | –                                                                      |
|                    |      |     |         |                                      |                                                                             |                | (+) Born outside the USA                                              | –                                                                      |
|                    |      |     |         |                                      |                                                                             |                | (+) Clinic location                                                   | –                                                                      |
|                    |      |     |         |                                      |                                                                             |                | (+) Higher medication-taking behaviour score                          | –                                                                      |
| Morisky et al[108] | 2003 | 5561| USA     | Retrospective cohort                  | Adolescents receiving TB infection treatment                             | 7              | (+) Younger age                                                       | (+) Asian ethnicity                                                |
| Muller et al[84]   | 2008 | 272 | Sweden  | Prospective cohort/contact investigation | Children and adolescents exposed to individuals with infectious TB        | 1,5,6          | –                                                                      | –                                                                      |
| Reference       | Year | N   | Country | Study type                      | Population                                 | Steps reported | Factors statistically associated with completion in children/adolescents | Factors descriptively associated with completion in children/adolescents |
|-----------------|------|-----|---------|---------------------------------|--------------------------------------------|----------------|------------------------------------------------------------------------|------------------------------------------------------------------------|
| Nuzzo et al96   | 2015 | 137 | USA     | Retrospective cohort            | Children* and adolescents tested for TB    | 4–7            | --                                                                     | --                                                                     |
| Olsson et al133 | 2018 | 84  | Sweden  | Retrospective cohort            | Children* and adolescents receiving TB infection treatment | 7              | --                                                                     | --                                                                     |
| Page et al117   | 2006 | 254 | USA     | Retrospective cohort            | Adolescents receiving TB infection treatment | 7              | --                                                                     | --                                                                     |
| Parsyan et al111| 2007 | 251 | USA     | Retrospective cohort            | Children* and adolescents receiving TB infection treatment | 7              | --                                                                     | --                                                                     |
| Parsaresh et al18 | 2018 | 14  | Australia | Retrospective cohort/contact investigation | Children exposed to a physician with infectious TB | 1–7          | --                                                                     | --                                                                     |
| Phillips et al19 | 2004 | 781 | USA     | Prospective cohort/contact investigation | Adolescents exposed to individuals with infectious TB | 1,5–7        | (−) Patient/caregiver refusal                                         | (−) Treatment with 4R (vs 6H or 9H)                                   |
| Plourde et al145| 2019 | 1926 | Canada  | Retrospective cohort            | Children* and adolescents receiving TB infection treatment | 7              | (−) Location of origin (Eastern Europe vs others)                     | (−) Patient/caregiver refusal                                        |
| Reicher et al102 | 2002 | 52  | USA     | Retrospective cohort            | Children* and adolescents exposed to individuals with infectious TB | 5–7          | (−) Moved out of catchment                                           | (−) Transferred care                                                  |
| Rinsky et al173  | 2018 | 26  | USA     | Prospective cohort/contact investigation | Neonates* exposed to a patient with infectious TB | 1,2,6        | (−) Unable to locate family                                           | (−) Unable to locate family                                          |
| Rogo et al158   | 2017 | 120 | USA     | Retrospective cohort            | Children* and adolescents receiving TB infection treatment | 7            | (−) Female                                                              | (+) Female                                                             |
|                 |      |     |         |                                 |                                            |                | (+) Interpreter used                                                   | (+) Interpreter used                                                  |
|                 |      |     |         |                                 |                                            |                | (+) Referral from within hospital                                     | (+) Referral from within hospital                                    |
|                 |      |     |         |                                 |                                            |                | (−) Medication adverse effects                                        | (−) Medication adverse effects                                        |
|                 |      |     |         |                                 |                                            |                | (−) Prior BCG vaccination                                              | (−) Prior BCG vaccination                                              |
| Ronald et al146  | 2020 | 2359 | Canada  | Retrospective cohort            | Children* and adolescents receiving TB infection treatment | 7            | (−) Treatment with 4R (vs 9H)                                         | (−) Treatment with 4R (vs 9H)                                        |
| Rubinowitz et al149 | 2014 | 3552 | Canada  | Retrospective cohort            | Children* and adolescents receiving TB infection treatment | 7            | (−) Treatment with 4R (vs 9H)                                         | (−) Treatment with 4R (vs 9H)                                        |

Continued
| Reference       | Year | N     | Country | Study type                     | Population                                                                 | Steps reported | Factors statistically associated with completion in children/adolescents | Factors descriptively associated with completion in children/adolescents |
|-----------------|------|-------|---------|--------------------------------|---------------------------------------------------------------------------|----------------|-----------------------------------------------------------------------|-----------------------------------------------------------------------|
| Sandul et al    | 2017 | 164   | USA     | Prospective cohort             | Children* and adolescents receiving TB infection treatment                | 7              | –                                                                     | (-) Medication adverse effects                                       |
| Santos et al    | 2020 | 72    | Portugal| Retrospective cohort           | Children* receiving TB infection treatment                                | 7 (±) Age <6 years (vs ≥6 years) | (+) Age <6 years (vs ≥6 years) | (-) Medication adverse effects                                       |
| Saunders et al  | 2014 | 13584 | UK      | Retrospective cohort/contact investigation | Children* and adolescents exposed to individuals with infectious TB        | 2              | –                                                                     | –                                                                     |
| Sentis et al    | 2020 | 1524  | Portugal| Retrospective cohort           | Children* and adolescents receiving TB infection treatment                | 7              | –                                                                     | –                                                                     |
| Seraphin et al  | 2019 | 3150  | USA     | Retrospective cohort           | Children* and adolescents receiving TB infection treatment                | 7              | –                                                                     | (-) Patient/caregiver refusal                                       |
| Sipan et al     | 2003 | 8028  | USA     | Prospective cohort             | Adolescent students undergoing scheduled screening                         | 1,2            | –                                                                     | –                                                                     |
| Sloot et al     | 2014 | 130   | The Netherlands | Retrospective cohort/contact investigation | Children* and adolescents exposed to individuals with infectious TB       | 1              | –                                                                     | –                                                                     |
| Song et al      | 2012 | 1826  | South Korea | Retrospective cohort/contact investigation | Adolescent students exposed to individuals with infectious TB            | 1,5-7          | –                                                                     | –                                                                     |
| Souder et al    | 2016 | 108   | USA     | Retrospective cohort/contact investigation | Children* and adolescents exposed to individuals with infectious TB       | 7              | –                                                                     | –                                                                     |
| Spicer et al    | 2013 | 1516  | USA     | Retrospective cohort           | Children* and adolescents diagnosed with TB infection                     | 5-7            | (+) Treatment at an offsite clinic (vs hospital clinic) (+) Younger age | (-) Patient/caregiver refusal                                       |
| Spruijt et al   | 2019 | 85    | The Netherlands | Prospective cohort and qualitative/survey | Children* and adolescents receiving TB infection treatment             | 7              | (+) Treatment with 4RH (vs 9H)                                       | (-) Early treatment termination by primary care provider (-) Lack of understanding of administration instructions (-) Medication adverse effects (-) Patient/caregiver refusal |
| Spyridis et al  | 2007 | 926   | Greece  | RCT                            | Children* and adolescents receiving TB infection treatment               | 7              | (+) Treatment with 4RH (vs 9H)                                       | (-) Early treatment termination by primary care provider (-) Lack of understanding of administration instructions (-) Medication adverse effects (-) Patient/caregiver refusal |
| Reference         | Year | N  | Country     | Study type      | Population                                                                 | Steps reported | Factors statistically associated with completion in children/adolescents | Factors descriptively associated with completion in children/adolescents |
|-------------------|------|----|-------------|-----------------|-----------------------------------------------------------------------------|----------------|------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Starr et al.      | 1999 | 42 | Australia   | Prospective cohort | Adolescents receiving TB infection treatment                               | 7              | -                                                                      | -                                                                       |
| Sterling et al.   | 2020 |    | -           | Systematic review  | Children* and adolescents receiving TB infection treatment                  | 7              | -                                                                      | -                                                                       |
| Stockbridge et al.| 2018 | 105| USA         | Retrospective cohort | Children* and adolescents receiving TB infection treatment                  | 7              | -                                                                      | -                                                                       |
| Taylor et al.     | 2016 | 8231| USA         | Retrospective cohort | Child* and adolescent immigrants receiving TB infection treatment           | 7              | -                                                                      | -                                                                       |
| Thee et al.       | 2019 | 301| Germany     | Prospective cohort  | Adolescent refugees                                                          | 5–7            | (-) Moved out of catchment                                           |                                                                         |
| van der Heijden et al. | 2015 | 9143| USA         | Retrospective cohort  | Children* and adolescents receiving outpatient primary care                  | 1–3            | (+) Older age                                                        |                                                                         |
| Venturini et al.  | 2018 | 441| Italy       | Retrospective cohort  | Children and adolescents receiving treatment                                 | 7              | (+) Treatment with 3–4HR (vs 6–9H)                                    |                                                                         |
| Vivier et al.     | 2006 | 1988| USA         | Retrospective cohort  | Children* tested for TB                                                      | 1,2            | (+) Head of household not a US citizen                               |                                                                         |
| Wang et al.       | 2010 | 72 | USA         | Prospective cohort/ contact investigation | Adolescent students exposed to individuals with infectious TB                 | 1              | (-) Moved out of catchment                                           |                                                                         |
**Table 1**  Characteristics of included studies

| Study type | Number of studies |
|------------|-------------------|
| Total included studies | 146 |
| Year published | |
| Before 2001 | 7 |
| 2001–2010 | 45 |
| 2011–2020 | 94 |
| Study type | |
| Systematic review | 3 |
| Retrospective cohort/cross-sectional studies | 84 |
| Cohort studies | 67 |
| Cross-sectional studies | 2 |
| Contact investigations (cohort+cross-sectional) | 15 |
| Prospective cohort/cross-sectional studies | 46* |
| Cohort studies | 20* |
| Cross-sectional studies | 6 |
| Contact investigations (cohort+cross-sectional) | 20 |
| Randomised trials | 7 studies/9 papers |
| Qualitative/survey | 5* |

*One study presented results of both a prospective cohort and qualitative/survey analysis.

**Table 2**  Characteristics of included studies

| Study characteristics | Number of studies |
|-----------------------|-------------------|
| Total included studies | 146 |
| Year published | |
| Before 2001 | 7 |
| 2001–2010 | 45 |
| 2011–2020 | 94 |
| Study type | |
| Systematic review | 3 |
| Retrospective cohort/cross-sectional studies | 84 |
| Cohort studies | 67 |
| Cross-sectional studies | 2 |
| Contact investigations (cohort+cross-sectional) | 15 |
| Prospective cohort/cross-sectional studies | 46* |
| Cohort studies | 20* |
| Cross-sectional studies | 6 |
| Contact investigations (cohort+cross-sectional) | 20 |
| Randomised trials | 7 studies/9 papers |
| Qualitative/survey | 5* |

Step 1: intended for testing → received a test

Twenty-two studies documented screening of paediatric patients at high risk of TB infection because of exposure in healthcare settings,\(^{38}^{44}\), the community,\(^{28}^{33}^{41}^{45}^{52}\) and schools.\(^{36}^{53}^{60}\) Additionally, 12 studies reported screening groups with a high population prevalence of TB infection, such as newly arrived asylum seekers, immigrants and refugees,\(^{37}^{61}^{64}\) and students from high-risk populations.\(^{39}^{40}^{65}^{69}\) Three studies reported on primary care based screening—two from the USA\(^{70}^{71}\) and one from the United Arab Emirates\(^{72}\)—all of which used risk

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1. Factors associated with increased retention.
2. Factors associated with decreased retention.
3. Included children <5-year-old.
4. Directly observed preventive treatment.
5. History of TB treatment.
6. Treatment for LTBI.
7. Tubercolosis skin test.
8. Retrospective cohort study.
9. Cross-sectional study.
10. Randomised trial.
11. Qualitative/survey.
12. Included patients living in low-income and middle-income countries.
13. Care cascade steps.
14. Comparative effectiveness studies targeting retention in the cascade.

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| Study type                          | Number of studies |
|-------------------------------------|-------------------|
| Total included studies              | 146               |
| Year published                      |                   |
| Before 2001                         | 7                 |
| 2001–2010                           | 45                |
| 2011–2020                           | 94                |
| Study type                          |                   |
| Systematic review                   | 3                 |
| Retrospective cohort/cross-sectional studies | 84         |
| Cohort studies                      | 67                |
| Cross-sectional studies             | 2                 |
| Contact investigations (cohort+cross-sectional) | 15       |
| Prospective cohort/cross-sectional studies | 46*       |
| Cohort studies                      | 20*               |
| Cross-sectional studies             | 6                 |
| Contact investigations (cohort+cross-sectional) | 20       |
| Randomised trials                   | 7 studies/9 papers |
| Qualitative/survey                  | 5*                |

*One study presented results of both a prospective cohort and qualitative/survey analysis.

**Step 1: intended for testing → received a test**

Twenty-two studies documented screening of paediatric patients at high risk of TB infection because of exposure in healthcare settings, the community and schools. Additionally, 12 studies reported screening groups with a high population prevalence of TB infection, such as newly arrived asylum seekers, immigrants and refugees, and students from high-risk populations. Three studies reported on primary care based screening—two from the USA and one from the United Arab Emirates—all of which used risk
Table 3  Facilitators and barriers affecting retention in the paediatric TB infection care cascade, interventions used and knowledge gaps

| Cascade step | Facilitators/factors associated with higher retention | Barriers/factors associated with lower retention | Interventions used | Knowledge gaps |
|--------------|------------------------------------------------------|------------------------------------------------|-------------------|----------------|
| 1) Intended for testing → initial testing | LMIC ▶ No analytic studies. | ► Caregiver non-acceptance. 66  ► Child non-acceptance/refusal. 66  ► Medical contraindications (concurrent infectious disease and chronic disease). 66 73  ► Low perceived risk. 49  ► Older age. 20  ► Patient mobility/inability to contact at-risk patients. 29 46 74 75  ► Test stock-outs. 61 74 | ► Multimodal solutions targeting knowledge, stigma and cost associated with diagnosis and treatment. 63  ► Contact tracing programmes. 49 50 96 81 74  ► School-based screening. 56 | ► Improving availability of TST and IGRA.  ► Populations at risk for low testing uptake.  ► Strategies to improve testing uptake.  ► Yield of primary care and community-based screening. |
|              | HIC ▶ Hospital-based and community health centre-based care. 76  ▶ Sociodemographic factors (language at home). 76 | ► Caregiver non-acceptance. 37  ► Child non-acceptance/refusal. 69  ► Patient mobility/inability to contact at-risk patients. 46 51 58 73  ► Older age. 70  ► Younger age. 72 | ► Contact tracing programs. 36 38 41 44–46 51 53–55 57–59 73 77  ► School-based screening. 36 93–95 97–98 70 | |
| 2) Initially tested → received test result | LMIC ▶ No analytic studies. | ► No analytic studies. | ► No analytic studies. | ► Comparison of TST and IGRA in loss to follow-up.  ► Reasons for loss to follow-up. |
|              | HIC ▶ Hospital-based and community health centre-based care. 76  ▶ Sociodemographic factors (language at home). 76 | ► Forgetfulness. 71  ► Older age. 79 70  ► Other sociodemographic factors (race/ethnicity; language; parent citizenship status). 91 70  ► Transportation/financial barriers. 71 | ► Home nursing follow-up. 77  ► Phone reminders. 71  ► Positive and negative reinforcements. 71 | |
| 3) Received test result → referral for evaluation | LMIC ▶ No analytic studies. | ► No analytic studies. | ► No analytic studies. | ► Reasons for loss to follow-up.  ► Strategies to strengthen referral process. |
|              | HIC ▶ No analytic studies. | ► No analytic studies. | ► No analytic studies. | |
| 4) Referral for evaluation → completion of evaluation | LMIC ▶ No analytic studies. | ► No analytic studies. | ► Symptom-based screening. 28 | ► Reasons for loss to follow-up.  ► Strategies to strengthen referral process. |
|              | HIC ▶ No analytic studies. | ► Location of family origin. 40  ► Moving prior to completion of medical evaluation. 78  ► Refusal of TB clinic visit. 40 | ► No analytic studies. | |
| 5) Completion of evaluation → recommendation for treatment | LMIC ▶ No analytic studies. | ► Medical contraindications (concurrent infectious disease). 102  ► Clinicians’ concerns about patients’ adherence. 103  ► Medical contraindications (medical instability/elevated transaminases). 98 | ► No analytic studies. | ► Prevalence of medical contraindications.  ► Strategies to shorten time between evaluation and recommendation. |
|              | HIC ▶ No analytic studies. | ► Medical contraindications (medical instability/elevated transaminases). 98 | ► No analytic studies. | |

Continued
| Cascade step | Facilitators/factors associated with higher retention | Barriers/factors associated with lower retention | Interventions used | Knowledge gaps |
|--------------|---------------------------------------------------|-----------------------------------------------|------------------|---------------|
| 6) Recommendation for treatment → initiation of treatment | | | | |
| LMIC | ► Knowledge about TB transmission, treatment and policy.104 | ► Concern about medication adverse effects.104 | ► No analytic studies. | ► Reasons for patient/caregiver refusal. |
| | ► Relationships with patients with TB.104 | ► Patient/caregiver refusal.104 | | |
| HIC | ► Refugees.64 | ► Country of origin.99 115 | | |
| | | ► Living in ‘blended families’.65 | | |
| | | ► Moving away/transferred care before starting therapy.83 95 | | |
| | | ► Patient/caregiver refusal.104 105 106 | | |
| 7) Initiation of treatment → completion of treatment | LMIC | ► Caregiver education.56 | ► Experience of or concerns about adverse medication effects.32 51 104 105 | ► Cash incentives.107 |
| | | ► Caregiver knowledge about TB infection and BCG.30 31 41 64 | | |
| | | ► Close relationship and close contact with TB index patients.112 | | |
| | | ► Personal health knowledge/beliefs.94 95 104 | | |
| | | ► Shorter therapy regimen.32 104 | | |
| | | ► Sociodemographic factors (Human Development Index).30 | | |
| HIC | ► Female sex.31 | ► Adverse home/family environment.125 | ► Adherence counselling/ coaching.106 107 | ► Benefits and downsides of joint therapy management between specialists and primary care providers. |
| | ► Family members undergoing TB testing.68 | ► Experience of or concerns about adverse medication effects.17 18 51 104 | ► Contingency contracting for adolescents.41 46 | |
| | ► Family support.119 | ► Delays in diagnostic steps.46 92 | ► DOPT.13 14 17 85 88 90 94 118 120 121 125 126 130 132 | |
| | ► History of receiving care at the clinic.50 | ► Caregiver work conflicts.135 | ► Income.107 108 109 118 120 121 125 126 129 | |
| | ► Location of origin.40 99 115 124 | ► Early discontinuation by physicians.36 126 | ► Home nursing assessments/outreach.133 | |
| | | ► Psychological well-being and perceived mastery.113 116 124 | | |
| | | ► Refugees.31 94 95 104 | | |
| | | ► School achievement.137 139 | | |
| | | ► Shorter therapy regimen.34 35 | | |
| | | ► Home medical contraindications (pregnancy and concurrent infectious disease).51 103 | | |
| | | ► Medical contraindications (pregnancy and concurrent infectious disease).51 103 | | |
| | | ► Movement away during treatment.88 93 103 105 119 124 | | |
| | | ► Patient/caregiver lack of knowledge about TB and treatment.51 | | |
| | | ► Other sociodemographic factors (eg, language at home, family composition and race/ethnicity).40 51 83 113 115 116 118 134 143 | | |
| | | ► Younger age.51 103 113 115 116 118 134 143 | | |

*Evaluated in comparative effectiveness studies.

DOPT, directly observed preventive treatment; HIC, high-income country; IGRA, interferon gamma release assay; LMIC, low-income and middle-income country; MDR, multidrug resistant; TB, tuberculosis; TST, tuberculin skin test.
screening questionnaires to identify paediatric patients for testing. Completion of testing varied widely, ranging from 28% to 100%. Several barriers to testing were common to high-income countries and LMICs. Lack of acceptability among caregivers for TST and IGRA often precluded testing, due to factors such as fear of blood draws (as in a cohort of asylum seekers in Denmark), and ‘parental avoidance’ in Iran. Low perceived risk also motivated caregivers to decline testing for their children. Children also refused testing. For example, among 5000 schoolchildren intended for testing in Iran, 220 ran away from the team before they could be tested. Contacting at-risk children and adolescents proved challenging in both high-income countries and LMICs. At-risk patients were often highly mobile, and families could be difficult to contact or locate. Additional patient/family-related factors that have been statistically associated with lack of testing included both older age and younger age, and presence of comorbidities.

Logistical and health system challenges to testing differed between high-income countries and LMICs. In LMIC, stock-outs of tuberculin limited ability to perform TSTs. Meanwhile, the setting of primary care delivery was found to affect testing uptake in the USA.

A number of studies in high-income countries and LMICs used contact tracing and targeted school-based screening to facilitate uptake of TB infection testing. Only one study specifically tested interventions to improve testing uptake—the aforementioned ACT4 cluster randomised trial, which found that a multimodal strategy increased identification and testing of paediatric contacts from a preintervention baseline in Ghana.

Step 2: received a test → test read

Twenty-seven studies documented completion of the second cascade step. All studies that presented completion of initial TB testing procedures used the proportion of TSTs that were read as their outcome. No studies documented methods to deliver IGRA results to patients or follow-up indeterminate IGRA results. Return for TST reading was mainly described in three contexts: (1) programmatic evaluations of school-based TB infection screening and treatment programmes; (2) non-school-based contact investigations; and (3) primary care clinics.

Most studies demonstrated high rates of return (>90%) following TST placement, although three studies conducted in primary care clinics in the USA documented lower return rates (58%–84%). No studies from LMIC reported specific facilitators or barriers to completion of the step. Four studies from high-income countries evaluated associations with TST reading, finding that demographic and care delivery related factors affected retention in this step of the cascade. A study of primary care patients in the USA noted that transportation-related and financial barriers precluded TST reading for some patients. One contact investigation of individuals exposed to adults with TB in the UK found that patients <16 years old were more likely than patients 16–64 years old to complete TB infection screening.

A study of paediatric patients screened for TB infection in a primary care practice in the USA found that TST non-completion was associated with non-Hispanic black race (vs other race/ethnicity), older age and earlier year of TST placement. Finally, young children enrolled in Medicaid in the USA had higher TST read rates if a parent was not a US citizen, if the primary language at home was not English or if care was delivered at a hospital-based clinic or community health centre.

We identified one study that examined strategies to improve return for TST reading, which was conducted among paediatric patients attending a US primary care clinic. In this study, families were randomised to one of five groups, including positive and negative reinforcement groups, and a home nurse-visit TST-reading group. Rates of TST reading in all groups, including control, were higher than in a prestudy baseline, which the authors suggest may have reflected a Hawthorne effect. The highest rate of return was 84% in the home TST reading group, although this study arm was discontinued early due to logistical challenges with the visiting nurses.

Step 3: test read → referred for medical evaluation

Fifteen studies documented completion of the third cascade step. In both high-income countries and LMICs, referral after a positive test occurred through contact investigations and mass screenings at schools with at-risk students, primary care clinics in the USA and among asylum seekers in Denmark. All studies documented high rates of referral (>97%). Though most referrals occurred when screening tests returned positive, two studies reported obtaining chest radiographs prior to referral. Of note, patients in most studies did not require referrals, because initial testing and subsequent medical evaluation were frequently conducted within a single care setting or by the same clinician. No studies from either high-income countries or LMICs assessed independent predictors, facilitators or barriers to referral or explored interventions targeting the referral process.

Step 4: referred for medical evaluation → completed medical evaluation

Twenty studies documented completion of the fourth cascade step. Most included studies defined the completion of medical evaluation as receiving a clinical exam and chest radiograph to exclude active TB after a positive TB infection test. Rates of medical evaluation completion were generally high (>90%), although five studies documented rates <90%. Notably, one study of nurse-led, school-based screening among an immigrant population in Israel found that only 29% of paediatric patients completed medical examinations.
Studies from high-income countries identified several barriers to evaluation completion. Family movement prevented completion of evaluation in two studies. Movement included transitions of care to outside clinics, which disrupted documentation of evaluation completion, as in a study of international adoptees in the USA. Movement also consisted of migration out of catchment areas, as in a review of a school-based TB screening programme in Switzerland, in which 2 of 21 paediatric patients with positive screening tests moved out of the country before evaluation could be completed. Caregiver refusal also acted as a barrier to completion of evaluation: a study of school-based screening in Canada found that of 724 paediatric patients with positive screening tests, 6% of patients/families ‘refused’ to visit a TB clinic for medical evaluation. No studies from LMIC documented reasons for non-completion of medical evaluation. However, a study from Uganda noted that reliance on chest radiograph to exclude TB disease may not be feasible in many settings due to lack of radiography equipment. Using chest radiograph as a gold standard, authors devised a score based on cough and reduced playfulness that could identify child contacts with high probability of having TB disease, enabling them to differentiate these patients from paediatric patients with TB infection or no TB infection following exposure to infected adults.

**Step 5: completed medical evaluation → treatment recommended**

Thirty-nine studies documented completion of the fifth cascade step. Most studies documented high (>90%) rates of recommendation to start treatment after completion of a medical examination. Only one study documented <90% recommendation rate: a study from Australia in which 86% of paediatric patients with TB infection were recommended to start treatment. The primary reason treatment was not recommended in high-income countries and LMIC was because providing treatment was not strictly indicated, for example, because of guidelines not supporting TB infection treatment for select patients with positive tests and presumed false-positive tests in the setting of prior BCG vaccination. Clinicians’ concerns about patients’ medical state and ability to adhere to medication were identified as reasons for not recommending treatment in LMIC. Medical reasons for deferring to recommend treatment included concurrent chronic infections in children in India and elevated transaminases and medical instability in exposed neonates in South Korea. In high-income countries, behaviour concerns precluded treatment recommendation. In a study of unaccompanied asylum seekers in Sweden, treatment was not recommended for some patients who were felt to be ‘psychologically unfit for treatment’. In this study, concerns about adherence arose from both perceived structural factors, such as likelihood of migrating out of catchment areas or becoming physically incarcerated or detained, and perceived psychological barriers to taking medication. No studies described interventions to improve retention at this step of the cascade.

**Step 6: treatment recommended → treatment started**

Forty-seven studies documented completion of the sixth cascade step. Rates of treatment initiation among patients for whom treatment was recommended ranged from 33% in a school-based contact investigation in the USA to 100% in several studies. In both high-income countries and LMICs, patient or caregiver refusal was a major barrier to treatment initiation. Patient and caregiver concerns about medication adverse effects were a common cause of treatment refusal. In addition, a study of adolescent student contacts in China assessed associations with accepting treatment and found that students with a higher level of knowledge about TB (measured by a knowledge and attitudes survey) and close contact with a TB patient were more likely to accept treatment. Patient demographic characteristics have been linked to treatment refusal in high-income countries. A report of a TB infection screening in largely immigrant classrooms in Canada found that immigrants from Eastern Europe had higher odds of treatment refusal (compared with immigrants from Southeast Asia, adjusted OR (aOR) 6.91 (95% CI 1.56 to 30.75)), as did children living with one parent and a parent in law (a ‘blended family’, compared with non-blended families’) (aOR 3.25 (95% CI 1.25 to 8.46)). One study of paediatric patients with TB infection referred to a US paediatric hospital found that patients born in Pacific Asia, Eastern Europe, and North Africa and the Middle East had treatment refusal rates >10%, compared with <10% among patients born in other regions, though statistical comparison was not performed. Among immigrants and refugees documented in the US Centers for Disease Control and Prevention (CDC) Electronic Disease Notification System, treatment initiation was ‘slightly greater’ in child refugees than child non-refugee immigrants. In studies from high-income countries, movement of patients was also linked to non-initiation of treatment. Two contact investigations in the USA noted that movement of patients out of clinical catchment areas and between care providers hindered documentation of treatment initiation. We did not identify studies from high-income countries or LMICs that tested strategies to improve treatment initiation after recommendation.

**Step 7: treatment started → treatment completed**

Most articles identified in our scoping review described treatment adherence or completion. Most studies were retrospective and single site, although some prospectively sought to assess interventions to improve treatment...
adherence, either through shorter courses of treatment or dedicated adherence promotion programmes.

Type and duration of treatment

Two reviews concluded that shorter duration TB infection treatment regimens (4 months of rifampin, 3 months of rifampin and isoniazid, and 3 months of isoniazid and rifapentine via directly observed preventive treatment (DOPT) for paediatric patients over 2 years old yield higher rates of completion than longer treatment regimens. The WHO has endorsed shorter duration rifamycin-based treatment regimens for children and adolescents <15 years old.

Few studies in our review examined adherence to regimens tailored to multidrug-resistant (MDR) TB infection. A contact investigation in the Federated States of Micronesia found that 42 of 43 paediatric patients completed 12 months of fluoroquinolone-based treatment. In contrast, three studies from high-income countries demonstrated high rates of treatment changes or discontinuation to a variety of medications due to adverse medication effects.

Several studies from both high-income countries and LMICs examined the timing of treatment discontinuation. These studies primarily evaluated 6 months or 9 months of isoniazid and used clinic return visits as a marker of adherence. Of patients who discontinued treatment, most stopped within the first 4 months.

Treatment delivery strategy

The most widely reported treatment delivery method in both high-income countries and LMICs was self-administered treatment (SAT) with isoniazid, prescribed at public health department or TB infectious diseases/chest clinics. DOPT was also frequently employed and universally used when patients were prescribed isoniazid plus rifapentine. Apart from treatment-specific use of DOPT, other indications for DOPT were inconsistent across studies, with some reserving DOPT for young patients or those perceived to be at high risk for, or have proven, non-adherence.

Two studies from the US directly compared treatment delivery strategies. The first compared health department-prescribed SAT with school-based DOPT, finding that SAT was associated with significantly lower rates of treatment completion compared with DOPT (50% vs 88%). The second found that receipt of 9 months of isoniazid or 6 months of rifampin via DOPT administered at a health department was associated with increased odds of treatment completion compared with SAT (aOR 7.29 (95% CI 5.7 to 23.6)). In this study, DOPT was used for infants, young children, recent immigrants and patients receiving treatment as part of contact investigations, while older paediatric patients not in one of these categories were eligible for SAT.

Four studies from high-income countries described TB infection treatment adherence among patients initially evaluated at public health clinics but who could then be followed by primary paediatricians. These studies did not attempt to analyse benefits and downsides of joint management models. While most programmes required monthly clinic return to refill prescriptions, a programme evaluation study in the USA described the effects of enabling public health nurses to perform once monthly home visits for patients of all ages receiving TB infection treatment to ameliorate transportation-related loss to follow-up. Home follow-up was found to be associated with improved adherence among all patients (aOR 2.94, 95% CI 2.23 to 3.71), although pediatric-specific ORs were not reported.

Barriers and facilitators of treatment completion

Many studies evaluated predictors of treatment completion among paediatric patients. Concerns about and experiences of medication adverse effects prevented treatment completion in both high-income countries and LMICs. Likewise, medical contraindications to treatment that occurred during treatment courses, such as pregnancy or intercurrent non-TB infections, occasionally prompted discontinuation. In studies from LMIC, additional factors associated with treatment completion included caregiver education and knowledge about TB infection, personal health knowledge and beliefs, lack of stigma and close relationships with TB contacts.

Studies from high-income countries have assessed patient and family characteristics associated with treatment completion. Identified factors associated with treatment completion include both younger age and older age, family characteristics (race/ethnicity, family composition, supportive family and home environments, school achievement), and school achievement. Meanwhile, patient/family movement away from catchment areas could interrupt treatment. Finally, knowledge and practice-related factors, including lack of caregiver knowledge about TB infection, confusion about treatment regimens and forgetfulness, were found to contribute to treatment discontinuation.

We included two mixed-methods or qualitative studies that assessed reasons for treatment non-adherence or non-completion. A survey study examined barriers to TB infection adherence among US adolescents enrolled in a peer-counselling and caregiver-training intervention. Barriers to treatment adherence existed for patients (lack of knowledge, missed visits, challenges with completing baseline TB infection evaluation and concern about side effects), caregivers (lack of knowledge, work conflicts, cost and concerns about side effects) and providers (lack of knowledge and resistance to recommendations). Research in Brazil found that lower monthly income, lower knowledge about TB transmission and BCG
protection and higher cost of transportation were independently associated with non-adherence at 2 months.81

Studies from high-income countries investigated health systems factors that facilitated or impeded adherence and treatment completion, including treatment location, history of receiving care at the relevant clinic and prescriber type. Two studies demonstrated that delays in diagnostic steps prior to treatment initiation were associated with decreased treatment completion.40 82 Treatment setting and services also could affect completion, although locations and effects were heterogeneous.99 108 Establishing longitudinal care within a clinic or health system was associated with treatment completion. For example, a study of TB infection treatment in a US community health centre found higher treatment completion rates among paediatric patients who had attended ≥2 well child checks at the clinic prior to treatment initiation.82 Two studies from Canada showed opposite effects of provider type on treatment completion, with one showing decreased odds of treatment completion when prescribers were primary care physicians,32 while the other found no difference in completion rates based on provider type.140

Behavioural strategies to optimise adherence and treatment completion

A prior review of reviews of IPT adherence promotion methods identified two reviews that included studies with paediatric patients, and each review included only a single study with children and adolescents.141 The authors concluded there was little evidence supporting effectiveness of specific paediatric TPT adherence promotion strategies, although integration of TB and HIV services might improve adherence.

We identified three trials of behavioural interventions targeting adolescents with TB infection, all of which took place in high-income countries.136 138 142 None of these trials demonstrated improvement in adherence or treatment completion, although some secondary outcomes were met. A trial to improve TB infection treatment adherence among adolescents receiving care at two US public health clinics randomised patients to one of four behavioural interventions: counselling from peers who had completed TB infection treatment, a negotiated caregiver-participant ‘contingency contract’ using incentives provided by caregivers as reward for adherence, both peer counselling and contingency contracting, or usual care.136 There was no significant difference in completion rates between arms, though a secondary analysis indicated that peer counselling was positively associated with three mediating variables on the path to treatment completion: medication-taking behaviour, perceived mastery and perceived self-efficacy (p<0.05 for all scales).134 135 136 Another trial, based on the Behavioural Ecological Model, randomised US adolescents to adherence coaching, self-esteem counselling or usual care. The study found that adolescents randomised to adherence coaching took more pills (via monthly self-report) than patients in the other two arms, although rates of treatment completion were low (38%–51%) and not different between groups.142 Finally, a follow-up trial in the USA assessed adherence peer counselling versus life skills peer counselling to optimise adherence (measured by self-reported isoniazid adherence, validated by urine metabolite detection) among adolescents.139 Treatment completion rates were low (37%–40%), and there was no significant difference in treatment completion between the two study arms, although in a secondary multivariable analysis, total time spent in counselling sessions was associated with pill taking.

We identified two interventional studies that targeted adherence behaviours in children, both from high-income countries. One study described a rewards-based structural behavioural intervention administered at a US department of health clinic, in which young children were given a toy for completing treatment each month.143 This system was associated with increased odds of treatment completion compared with a historical cohort who did not receive incentives (aOR 2.42 (95% CI 1.66 to 3.51)). The second study compared 6-month or 9-month isoniazid treatment completion between patients of all ages, including children.131 Those patients deemed at high risk of treatment discontinuation were selected to receive monthly home nursing follow-up, while the remainder were followed monthly in clinic. Treatment completion rates were higher among patients assigned to home nursing follow-up across all groups (95.7% vs 92.1% for children <6 years old, and 93.1% vs 84.1% for patients aged 6–17 years old).

Additional interventions have been implemented to improve adherence among children and adolescents in high-income countries and LMICs, but effectiveness was not assessed against a control group. These include use of telemedicine DOPT,127 provision of free medications,119 adherence counselling,31 small cash incentives107 and multimodal interventions that adjust treatment regimens and delivery strategies to patients’ needs and attempt to individually address social/structural barriers to adherence.88 125

DISCUSSION

We identified a large literature describing steps of the TB infection care cascade for paediatric patients. Three key themes relating to the state of this literature are apparent from our review. First, most studies focused on the final cascade step: initiation to completion of treatment. Comparatively, little research has addressed steps leading to treatment initiation, despite evidence that up to 70% of patients who could benefit from TB infection treatment never start medication.3 Second, while studies identified heterogeneous factors associated with attrition from different cascade steps, identified factors were primarily related to patient/family characteristics. Few studies sought to identify health systems-related factors associated with cascade completion. Third, while
a number of studies have described behavioural interventions to improve retention, data supporting the efficacy of these interventions are scant.

While studies have identified facilitators and barriers to completion of the initial six steps of the TB infection care cascade, identified barriers vary between steps and study sites. Many studies described non-specific loss to follow-up as a primary reason for attrition. Qualitative and mixed methods analyses have been used to understand loss to follow-up among persons living with HIV and could help to examine loss to follow-up among children and adolescents evaluated and treated for TB infection. We identified only one comparative efficacy trial targeting a step prior to treatment initiation, which showed qualified support for strategies to improve return after TST placement in a high-resource setting.71

Research from both high-resource and resource-limited settings has extensively investigated barriers and facilitators of treatment adherence and completion (step 7). Robust data demonstrate tolerability and improved completion rates with shorter courses of rifamycin-based treatment, compared with 6-month or 9-month isoniazid regimens.14 35 105 106 120 145 146 In response to these data, both the WHO and the US CDC now recommend short-course treatments for TB infection.22 105 Trials of specific behavioural strategies to promote treatment adherence and completion have been less successful. Several key knowledge gaps remain to improve retention in the final step of the cascade, including: the scalability of promising pilot interventions; effects of specialist versus paediatric primary care teams; potential for mobile health technologies (mHealth) to optimise adherence;27 utility of targeting interventions towards paediatric patients, caregivers or both; and specific barriers and facilitators of adherence in resource-limited settings.

In our review, identified system-level factors included type of care setting, provider type, clinical wait times, availability of interpreters and other clinical support staff, availability of testing and treatment, and time and financial cost of diagnosis and treatment. Published studies described contradictory conclusions about the direction of some of these factors’ effects. For example, in studies examining the role of primary care providers and specialists in ensuring adherence to TB infection treatment, patients who receive prescriptions from generalists were more likely,99 equally likely32 or less likely32 to complete treatment than patients receiving treatment from specialists. One limitation of this literature is the reliance on data from single (mostly specialty) clinical settings, despite the fact that patients may transition between care settings for different steps of the care cascade. Research is needed to identify how to retain children and adolescents as they transition between community clinics, hospitals, specialty clinics, health department clinics and other care settings while navigating the cascade.

Few studies in our review assessed cascade completion among children and adolescents living with HIV, and we did not identify specific barriers or facilitators to these patients’ retention in the care cascade. Notably, per WHO and country-specific guidance, children and adolescents living with HIV exposed to TB are not uniformly tested for TB infection prior to initiation of TPT,22 and studies reporting on these children may have been excluded from our review. In analyses that included adults with HIV, people living with HIV have been found to have higher rates of treatment completion than comparison groups.19 20 32

Children and adolescents in LMIC face unique barriers to retention in the care cascade. There remains a wide policy-practice gap in identifying those at high risk for TB disease and with TB infection, and active contact tracing and case finding in LMIC remain critical areas for improvement.147 Additionally, a limited supply of TB infection tests hampers efforts to diagnose high-risk children and adolescents.61 74 148 Strategies to reduce cost and increase access to TST and IGRA in LMIC are needed to identify children and adolescents who would most benefit from TPT, including those not identified through contact tracing.

A sizeable body of research has investigated TPT adherence in LMIC administered as part of contact management. Although our review identified considerable literature on treatment completion, our requirement for TB infection testing inherently omitted several papers on TPT from LMIC in which infection testing was not done, per WHO guidelines.22 Drawing from literature excluded from our study, the prior review of contact case management in high-burden countries identified several barriers to completion of child contact management that overlap with our findings, including barriers posed by health systems, knowledge and attitudes, stigma, resource constraints, and treatment characteristics and adverse effects.23 To highlight valuable explanatory research on TPT from LMIC included in that prior review and published subsequently, qualitative and mixed-methods studies have illustrated how (lack of) knowledge,149–152 stigma,152–154 patient/caregiver and health system resource constraints,151 152 and combinations of these factors156 conspire to impede TPT initiation and completion in LMIC.

Several large, ongoing studies and programmes seek to scale interventions to improve cascade retention in LMIC. Examples include projects to increase rifapentine access for people living with HIV and child contacts <5 years old156; that test and scale novel approaches to TB diagnostics and retention in care;157 and that use the TB infection care cascade as a framework to identify step-specific, locally tailored interventions to improve retention.42 43 158 Additional studies to improve TPT initiation among child contacts in LMIC have shown promising results of socioeconomic support,148 enhanced contact investigation procedures48 and multilevel community interventions.156

Our analysis suggests several theory-based and methodological strategies to strengthen future research and programme implementation to improve retention
in the TB infection care cascade. First, behavioural theory can help structure intervention design and evaluation. In our review, there was sporadic use of established behavioural theories in building interventions to improve the cascade, and theory was only employed to understand and modify the final cascade step. Application of behavioural and organisational theory to upstream cascade steps is needed. For instance, behavioural theories may yield insights and testable solutions to caregivers’ refusal of TB infection testing for their children. Implementation science theory, models and frameworks may also prove useful in addressing barriers for a number of steps, such as improving health systems to mitigate loss to follow-up during transitions of care. Additionally, although recent literature has increasingly used quality improvement methods to address TB infection care, we did not identify any studies that used these methods to iteratively test and improve interventions.

Our review has several limitations. First, we did not attempt to survey the extensive literature on patients who received TPT following contact with individuals with infectious TB but who were not tested for TB infection. Despite the extensive research we identified describing the final cascade step, this research mostly took place in high-resource settings. Additional research from LMIC on supporting child contacts undergoing TPT who were not tested for TB infection has been summarised in detail in the prior case management review, though expanding testing capacity in LMIC remains a critical gap. Second, while broad, our search strategy may not have captured all pertinent literature on the cascade. Likewise, our language restrictions may have excluded relevant studies. Third, we did not perform a quality assessment of articles because of the heterogeneity of study types and because we chose to focus on exploring all insights the literature had to offer, as is common in scoping reviews. Fourth, a single reviewer assessed all studies, although any points of ambiguity were discussed among all authors. Finally, while the care cascade we used provides a useful framework to understand processes for diagnosing and treating TB infection, there is heterogeneity in local and international TB infection treatment guidance and practice, and not all steps are used in all settings. Our study also has several strengths. We identified studies from a range of geographic and care delivery settings, describing a variety of paediatric populations. We also identified studies that included unique populations, such as paediatric patients with MDR TB infection, infants, adolescents and refugees/asylum seekers.

In conclusion, our scoping review identified key gaps in understanding the paediatric TB infection care cascade. Future research should target knowledge gaps in the early steps of the cascade and identify modifiable health systems factors associated with cascade attrition. Future interventions should aim to be sustainable, theory-grounded, iteratively optimised and locally relevant.

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