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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 low-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.

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.

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]

A prior systematic review and meta-analysis found that more than 80% of adults and children at risk for TB infection do not complete the care cascade.[3] Several studies have found that children face different barriers and complete one or more cascade steps at different rates than adults.[12–20] Yet two prior systematic reviews of the TB infection

care cascade have either excluded children or did not distinguish the unique challenges paediatric patients face.[3 21] 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]

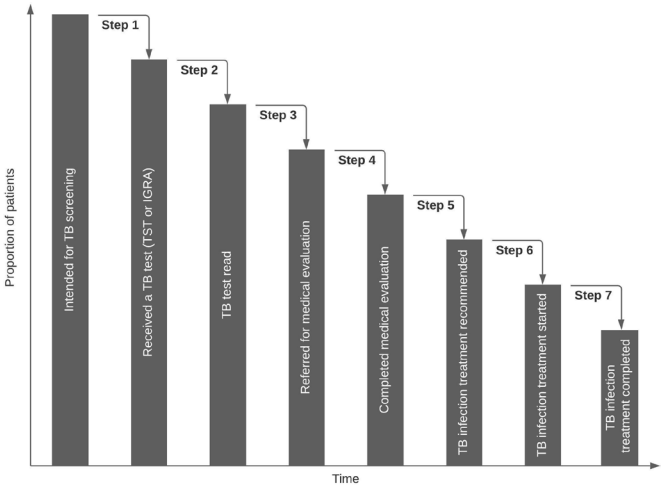

Figure 1 Schema of the TB infection care cascade (bars not to scale). IGRA, interferon gamma release assay; TB, tuberculosis; TST, tuberculin skin test.

Our study complements the prior review of the contact case management approach used in many LMIC[23] 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, 31 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.

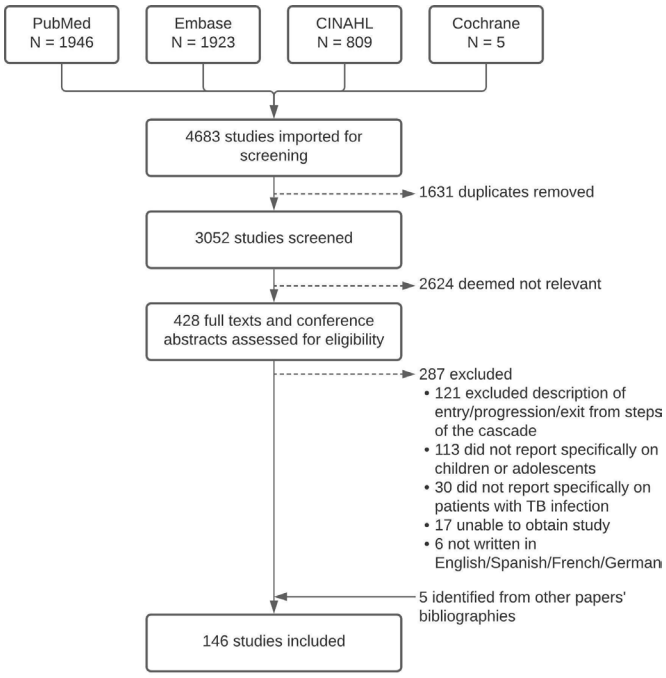

Figure 2 PRISMA diagram of evaluated and included studies. CINAHL, Cumulative Index to Nursing and Allied Health Literature; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TB, tuberculosis.

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] The proportion of paediatric patients who completed or appropriately exited the care cascade ranged from 65% in a large study of US high school students[39] 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[66]	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*[87]	2015	228	Brazil	Retrospective cohort	Children* and adolescents exposed to individuals with infectious TB	5–7	–	–
Baliashvili *et al*[50]	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*[107]	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*[43]	2020	225 (includes adults)	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[52]	2014	70	Colombia	Prospective cross-sectional/contact investigation	Children* exposed to individuals with infectious TB	1,7	(–) Male sex (+) Insured	–
Bonnet *et al*[28]	2017	339	Uganda	Prospective cohort	Children* exposed to individuals with infectious TB	1–7	–	–
Chakhaia *et al*[161]	2014	83	Georgia	Retrospective cohort/ contact investigation	Children* exposed to individuals with infectious TB	7	–	–
Coprada *et al*[74]	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

Continued

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
Diallo *et al*[93]	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[162]	2016	158	Brazil	Retrospective cohort	Children* and adolescents receiving TB infection treatment	7	–	–
Dorjee *et al*[102]	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*[29]	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*[112]	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*[61]	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*[56]	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*[49]	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*[163]	2018	61	North Macedonia	Retrospective cohort	Children* and adolescents receiving TB infection treatment	7	–	–

Continued

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
Khalid *et al*[75]	2020	3226	Sudan	Prospective cross-sectional	Child and adolescent students undergoing scheduled screening	1	–	(–) Absenteeism (–) Chronic disease (–) Unwillingness to participate
Li *et al*[104]	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*[136]	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*[164]	2009	47	Brazil	Prospective cohort	Children* and adolescents exposed to individuals with infectious TB	7	–	–
Mendonca *et al*[30]	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	–

Continued

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*[33]	2019	398	Tanzania	Prospective cohort	Children* exposed to individuals with infectious TB	1,5,6	–	(–) Caregiver refusal
Silva *et al*[81]	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	(–) Patient/caregiver refusal
Soussi *et al*[165]	2013	25	Tunisia	Retrospective cohort/ contact investigation	Children* exposed to individuals with infectious TB	1,6	–	–
van Zyl *et al*[34]	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*[35]	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*[67]	2017	1330041	China	Retrospective cohort	Adolescent students undergoing scheduled screening	1,5–7	–	–
Wong and Lee[79]	2020	439	Malaysia	Prospective cross-sectional	Child* and adolescent students undergoing scheduled screening	1–4	–	–
Wysocki *et al*[47]	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*[141]	2014	–	–	Systematic review of systematic reviews	Children* and adolescents initiating TPT	7	–	–

Continued

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
Adler-Shohet *et al*[36]	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*[37]	2020	224	Denmark	Retrospective cohort	Children* and adolescents seeking asylum	1–7	–	(–) Patient/caregiver refusal (–) Fear of blood draws
Ahn *et al*[38]	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*[72]	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*[44]	2011	103	Slovenia	Prospective cohort/ contact investigation	Neonates* exposed to an HCW with infectious TB	1,2	–	–
Anaraki *et al*[55]	2018	291	UK	Prospective cohort/ contact investigation	Adolescent students exposed to individuals with infectious TB	1	–	–
Assefa *et al*[106]	2018	–	–	Systematic review	Children* and adolescents receiving TB infection treatment	7	(+) Treatment with 3RH (vs 6H) (+) Treatment with 4RH (vs 9H)	–
Bennet and Eriksson[103]	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*[166]	2014	546	USA	Retrospective cohort	Adolescent refugees	6,7	–	–
Berlioz *et al*[46]	2008	1813	France	Prospective cohort/ contact investigation	Children* receiving outpatient primary care	1–6	–	(–) Inability to contact by mail (–) Patient/caregiver refusal (–) Adverse medication effects
Bibi *et al*[65]	2002	28 016	Israel	Retrospective cohort	Adolescent immigrants	1–5	–	–
Bieberly and Ali[13]	2008	47	USA	Retrospective cohort	Children* and adolescents receiving TB infection	7	–	(+) Age <12 years (vs older ages)
Bishara *et al*[88]	2015	220	Israel	Retrospective cohort	Child* and adolescent immigrants	5–7	(–) Age <5 years	–
Blumberg *et al*[167]	2005	286	USA	Prospective cohort	Adolescents receiving TB infection treatment	7	–	–

Continued

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 al*[4]	1999	446	USA	Prospective cohort	Children* and adolescents undergoing TB screening	2	–	–
Boyd *et al*[101]	2017	88	Australia	Retrospective cohort	Children* and adolescents diagnosed with TB infection	5–7	–	(–) Moved out of catchment
Brassard and Lamarre[51]	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 (–) Lack of cooperation from child (–) Concurrent infectious diseases
Brassard *et al*[68]	2006	3710	Canada	Prospective cohort	Child* and adolescent immigrants	1–4,7	(+) More family members undergoing TB testing (–) Older age at time of screening (–) Longer time since immigration	(–) Patient/caregiver refusal (–) Moved out of catchment
Breuss *et al*[86]	2002	34	Switzerland	Retrospective cohort	Children and adolescents seeking asylum	4	–	–
Bright-Thomas *et al*[168]	2010	334	UK	Retrospective cohort	Children* and adolescents receiving TB infection treatment	7	–	–
Calder *et al*[57]	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 al*[89]	2015	3	Spain	Retrospective cohort	Children and adolescents receiving anti-TNFα therapy	5–7	–	–
Cass *et al*[143]	2005	1582	USA	Prospective cohort	Children* and adolescents receiving TB infection treatment	7	(+) Spanish speaking (+) Contact investigation (+) Incentive programme (–) Clinic location (–) Missed appointment calls and letters (–) Referred to a public health nurse	–

Continued

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
Catho *et al*[169]	2015	43	France	Retrospective cohort/ contact investigation	Children* and adolescents exposed to individuals with infectious MDR-TB	7	–	–
Chang *et al*[131]	2013	1525	USA	Retrospective cohort	Children* and adolescents diagnosed with TB infection	7	(+) Home follow-up (vs clinic follow-up)	–
Chang *et al*[83]	2014	1872	USA	Retrospective cohort	Children* and adolescents diagnosed with TB infection	4–7	(–) Older age (–) Non-Hispanic race (–) Adverse medication effects	(–) Transferred care (–) Moved out of catchment (–) 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*[170]	1996	37	USA	Prospective cohort	Children* and adolescents screened for TB infection	2	–	–
Christy *et al*[80]	1996	401	USA	Prospective cross-sectional	Children* and adolescents receiving outpatient primary care	2	–	–
Coly and Morisky[113]	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*[114]	2015	16 995	USA	Retrospective cohort	Children* and adolescents tested for TB	7	–	–
Cruz *et al*[109]	2014	40	USA	Retrospective cohort	Children* and adolescents receiving TB infection treatment	7	–	(–) Medication adverse effects
Cruz and Starke[132]	2013	1383	USA	Retrospective cohort	Children* and adolescents receiving TB infection treatment	7	–	(–) Medication adverse effects (–) Moved out of catchment (–) Patient/caregiver refusal
Cruz and Starke[118]	2014	404	USA	Retrospective cohort	Children* and adolescents receiving TB infection treatment	7	(+) Treatment with 4R (vs 9H)	(–) Medication adverse effects (–) Moved out of catchment (–) Patient/caregiver refusal
Cruz and Starke[90]	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*[133]	2011	58	USA	Retrospective cohort	Children* and adolescents receiving TB infection treatment	7	–	(–) Medication adverse effects (–) Pregnancy

Continued

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*[91]	2004	92	France	Retrospective cohort	Children* and adolescents receiving TB infection treatment	5,6	–	–
Dewan *et al*[92]	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*[127]	2019	7	USA	Prospective cohort	Children receiving TB infection treatment	7	–	(+) Telemedicine DOPT
Elliot *et al*[94]	2018	36	Australia	Retrospective cohort	Child* and adolescent refugees	5–7	–	(–) Inability to contact families
Erkens *et al*[171]	2014	1120	The Netherlands	Retrospective cohort	Children* and adolescents diagnosed with TB infection	7	–	(–) Transferred care
Erkens *et al*[134]	2016	3301	The Netherlands	Retrospective cohort	Children* and adolescents diagnosed with TB infection	7	–	(–) Medication adverse effects
Fathoala *et al*[172]	2006	130	UK	Retrospective cohort	Children* and adolescents diagnosed with TB infection	7	–	–
Feja *et al*[108]	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*[120]	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*[129]	2017	213	Spain	Retrospective cohort	Children* and adolescents receiving TB infection treatment	7	–	–
Hatzenbuehler *et al*[39]	2016	925	USA	Prospective cohort	Adolescent students undergoing scheduled screening	1–7	–	–

Continued

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[63]	2018	ND	USA	Retrospective cohort	Adolescent refugees	7	–	(+) Age 13–17 years
Higuchi *et al*[173]	2008	43	Japan	Prospective cohort/ contact investigation	Child and adolescent students exposed to individuals with infectious TB	7	–	–
Hill *et al*[135]	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*[110]	2010	347	Canada and USA	Retrospective cross-sectional	Children* and adolescents receiving TB infection treatment	7	–	(–) Patient/caregiver refusal
Hovell *et al*[137]	2003	286	USA	Qualitative/survey	Adolescents receiving TB infection treatment	7	(+) Adherence coaching (+) Bicultural (+) School grades (+) Younger age (–) Risk-taking behaviours	–
Hovell *et al*[139]	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

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
Hovell *et al*[142]	2003	286	USA	RCT	Adolescents receiving TB infection treatment	7	(+) Adherence coaching (+) Bicultural (+) Younger age (–) Risk-taking behaviours	–
Hwang *et al*[45]	2019	269	South Korea	Retrospective cohort/ contact investigation	Children* and adolescents exposed to individuals with infectious TB	1,7	–	–
Iroh Tam *et al*[174]	2010	13	Ireland	Retrospective cohort	Children* and adolescents diagnosed with TB infection	7	–	–
Kaiser *et al*[95]	2015	215	USA	Prospective cohort/ contact investigation	Adolescent students exposed to individuals with infectious TB	2,5,6	–	–
Kim *et al*[53]	2017	947	South Korea	Retrospective cohort/ contact investigation	Adolescent students exposed to individuals with infectious TB	1,5,6	–	–
Kohn *et al*[85]	1996	864	USA	Prospective cohort	Adolescent students undergoing scheduled screening	4,7	(+) DOPT (vs SAT)	(–) Patient/caregiver refusal
Kominski *et al*[115]	2007	794	USA	RCT/cost effectiveness	Children and adolescents receiving TB infection treatment	7	(+) Living with both parents (+) Born outside of the USA	–
Kondo and Ito[96]	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*[121]	2008	132	USA	Retrospective cohort	Children and adolescents receiving TB infection treatment	7	-	–
Lardizabal *et al*[122]	2006	348	USA	Retrospective cohort	Children* and adolescents receiving TB infection treatment	7	–	–
Levesque *et al*[175]	2004	ND	Canada	Retrospective cohort	Child and adolescent refugees	1	–	–
Li *et al*[14]	2010	4119	USA	Retrospective cohort	Children and adolescents receiving TB infection treatment	7	–	(+) Treatment with 6R (vs 9H)

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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
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*[128]	2018	85	USA	Retrospective cohort	Children and adolescents receiving TB infection treatment	7	–	–
Martínez-Roig *et al*[178]	2003	73	Spain	Retrospective cohort	Children* and adolescents diagnosed with TB infection or exposed to individuals with infectious TB	7	–	–
Milinkovic *et al*[15]	2018	93	Canada	Retrospective cohort	Children and adolescents diagnosed with TB infection	6,7	–	–
Minodier *et al*[40]	2010	4375	Canada	Prospective cohort	Child and adolescent students undergoing scheduled screening	1–7	(+) Location of origin (–) Delay between TST and first clinic visit (–) Household composition (living with parents plus grandparents; living with non-child relatives) (–) Age >16 years (vs younger)	(–) Patient/caregiver refusal (–) Transferred care
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*[138]	2003	5561	USA	Retrospective cohort	Adolescents receiving TB infection treatment	7	(+) Younger age (+) Asian ethnicity	–
Muller *et al*[54]	2008	272	Sweden	Prospective cohort/contact investigation	Children and adolescents exposed to individuals with infectious TB	1,5,6	–	–

Continued

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
Nuzzo *et al*[16]	2015	137	USA	Retrospective cohort	Children* and adolescents tested for TB	4–7	–	–
Olsson *et al*[123]	2018	84	Sweden	Retrospective cohort	Children* and adolescents receiving TB infection treatment	7	–	–
Page *et al*[117]	2006	254	USA	Retrospective cohort	Adolescents receiving TB infection treatment	7	–	–
Parsyan *et al*[111]	2007	251	USA	Retrospective cohort	Children* and adolescents receiving TB infection treatment	7	–	–
Parvaresh *et al*[41]	2018	14	Australia	Retrospective cohort/ contact investigation	Children* exposed to a physician with infectious TB	1–7	–	–
Phillips *et al*[59]	2004	781	USA	Prospective cohort/ contact investigation	Adolescents exposed to individuals with infectious TB	1,5–7	–	(–) Patient/caregiver refusal
Plourde *et al*[145]	2019	1926	Canada	Retrospective cohort	Children* and adolescents receiving TB infection treatment	7	–	(–) Treatment with 4R (vs 6H or 9H)
Powell *et al*[124]	2008	545	USA	Retrospective cohort	Children and adolescents receiving TB infection treatment	7	(–) Location of origin (Eastern Europe vs others)	(–) Patient/caregiver refusal (–) Moved out of catchment (–) Transferred care
Reichler *et al*[98]	2002	52	USA	Retrospective cohort	Children* and adolescents exposed to individuals with infectious TB	5–7	–	–
Rinsky *et al*[73]	2018	26	USA	Prospective cohort/ contact investigation	Neonates* exposed to a patient with infectious TB	1,2,6	–	(–) Unable to locate family
Rogo *et al*[31]	2017	120	USA	Retrospective cohort	Children* and adolescents receiving TB infection treatment	7	–	(+) Female (+) Interpreter used (+) Referral from within hospital (+) Refugee (–) Medication adverse effects (–) Prior BCG vaccination
Ronald *et al*[140]	2020	2359	Canada	Retrospective cohort	Children* and adolescents receiving TB infection treatment	7	–	(+) Treatment with 4R (vs 9H)
Rubinowitz *et al*[32]	2014	3552	Canada	Retrospective cohort	Children* and adolescents receiving TB infection treatment	7	–	–

Continued

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
Sandul *et al*[17]	2017	164	USA	Prospective cohort	Children* and adolescents receiving TB infection treatment	7	–	(–) Medication adverse effects (–) Patient/caregiver refusal (–) Refusal of DOPT
Santos *et al*[125]	2020	72	Portugal	Retrospective cohort	Children* receiving TB infection treatment	7	(+) Age <6 years (vs ≥6 years)	(–) Medication adverse effects (–) 'Social problems/family dysfunction'
Saunders *et al*[125]	2014	13 584	UK	Retrospective cohort/ contact investigation	Children* and adolescents exposed to individuals with infectious TB	2	–	–
Sentis *et al*[179]	2020	1524	Portugal	Retrospective cohort	Children* and adolescents receiving TB infection treatment	7	–	–
Seraphin *et al*[19]	2019	3150	USA	Retrospective cohort	Children* and adolescents receiving TB infection treatment	7	–	(–) Patient/caregiver refusal (–) Medication adverse effects
Sipan *et al*[69]	2003	8028	USA	Prospective cohort	Adolescent students undergoing scheduled screening	1,2	–	–
Sloot *et al*[77]	2014	130	The Netherlands	Retrospective cohort/ Contact investigation	Children* and adolescents exposed to individuals with infectious TB	1	–	–
Song *et al*[60]	2012	1826	South Korea	Retrospective cohort/ contact investigation	Adolescent students exposed to individuals with infectious TB	1,5–7	–	–
Souder *et al*[130]	2016	108	USA	Retrospective cohort/ contact investigation	Children* and adolescents exposed to individuals with infectious TB	7	–	–
Spicer *et al*[99]	2013	1516	USA	Retrospective cohort	Children* and adolescents diagnosed with TB infection	5–7	(+) Treatment at an offsite clinic (vs hospital clinic) (+) Younger age (–) Location of origin	(–) Patient/caregiver refusal
Spruijt *et al*[180]	2019	85	The Netherlands	Prospective cohort and qualitative/survey	Children* and adolescents receiving TB infection treatment	7	–	–
Spyridis *et al*[126]	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

Continued

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
Starr *et al*[181]	1999	42	Australia	Prospective cohort	Adolescents receiving TB infection treatment	7	–	–
Sterling *et al*[105]	2020	–	–	Systematic review	Children* and adolescents receiving TB infection treatment	7	–	–
Stockbridge *et al*[20]	2018	105	USA	Retrospective cohort	Children* and adolescents receiving TB infection treatment	7	–	–
Taylor *et al*[64]	2016	8231	USA	Retrospective cohort	Child* and adolescent immigrants receiving TB infection treatment	7	–	–
Thee *et al*[100]	2019	301	Germany	Prospective cohort	Adolescent refugees	5–7	–	(–) Moved out of catchment
Usemann *et al*[78]	2019	1462	Switzerland	Retrospective cohort	Child and adolescent immigrants	2–4	–	(–) Moved out of catchment
van der Heijden *et al*[70]	2015	9143	USA	Retrospective cohort	Children* and adolescents receiving outpatient primary care	1–3	(+) Older age (+) Race/ethnicity (non-Hispanic black vs others) (+) Year of TST placement	–
Venturini *et al*[146]	2018	441	Italy	Retrospective cohort	Children and adolescents receiving treatment TB infection treatment	7	(+) Treatment with 3–4HR (vs 6–9H)	–
Vivier *et al*[76]	2006	1988	USA	Retrospective cohort	Children* tested for TB	1,2	(+) Head of household not a US citizen (+) Primary language other than English (+) Receiving care at a community health centre or hospital-based clinic (vs office-based practice)	–
Wang *et al*[58]	2010	72	USA	Prospective cohort/ contact investigation	Adolescent students exposed to individuals with infectious TB	1	–	(–) Moved out of catchment (–) Patient/caregiver refusal

Continued

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
Young *et al*[82]	2012	157	USA	Retrospective cohort	Children* and adolescents receiving outpatient primary care	3–7	(+) ≥2 well-child checks at health centre prior to TST (vs 0–1) (+) Fewer days between TST read and chest X-ray (+) Younger age	(–) Medication adverse effects

(+) Factors associated with increased retention.
(–) Factors associated with decreased retention.
*Included children <5 years old.
DOPT, directly observed preventive treatment; 6H, 6 months of isoniazid; 9H, 9 months of isoniazid; 6–9H, 6–9 months of isoniazid; HCW, healthcare worker; 3HP, 3 months of isoniazid plus rifapentine; 3HR, 3 months of isoniazid plus rifampin; 3–4HR, 3–4 months of isoniazid plus rifampin; IPT, isoniazid preventive treatment; MDR-TB, multidrug-resistant tuberculosis; ND, not documented; 4R, 4 months of rifampin; RCT, randomised controlled trial; SAT, self-administered treatment; TB, tuberculosis; TNFα, tumour necrosis factor alpha; TPT, TB preventive treatment; TST, tuberculin skin test.

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*
Included patients living in low-income and middle-income countries	31
Care cascade steps	
1 - Intended for testing → initial testing	44
2 - Initially tested → received test result	27
3 - Received test result → referral for evaluation	15
4 - Referral for evaluation → completion of evaluation	20
5 - Completion of evaluation → recommendation for treatment	39
6 - Recommendation for treatment → initiation of treatment	47
7 - Initiation of treatment → completion of treatment	105
1–7 - Entire cascade	7
Comparative effectiveness studies targeting retention in the cascade	21

*One study[180] 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,[38 44] the community[28 29 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

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 75] ▶ Low perceived risk.[49] ▶ Older age[50]. ▶ Patient mobility/inability to contact at-risk patients.[29 49 74 75] ▶ Test stock-outs.[61 74]	▶ Multimodal solutions targeting knowledge, stigma and cost associated with diagnosis and treatment.*[43] ▶ Contact tracing programmes.[49 50 56 61 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 53–55 57–60]	
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]	▶ Forgetfulness.[71] ▶ Older age.[18 70] ▶ Other sociodemographic factors (race/ethnicity; language; parent citizenship status).[70 76] ▶ Transportation/financial barriers.[71]	▶ Home nursing follow-up.*[71] ▶ 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] ▶ Transitioning care to other facilities.[84]	▶ No analytic studies.	
5) Completion of evaluation → recommendation for treatment	LMIC	▶ No analytic studies.	▶ Medical contraindications (concurrent infectious disease).[102]	▶ No analytic studies.	▶ Prevalence of medical contraindications. ▶ Strategies to shorten time between evaluation and recommendation.
	HIC	▶ No analytic studies.	▶ Clinicians' concerns about patients' adherence.[103] ▶ Medical contraindications (medical instability/elevated transaminases).[38]	▶ No analytic studies.	

Continued

Table 3 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] ▶ Relationships with patients with TB.[104]	▶ Concern about medication adverse effects.[104] ▶ Patient/caregiver refusal.[33 81 93 102]	▶ No analytic studies.	▶ Reasons for patient/caregiver refusal. ▶ Strategies to improve treatment uptake. ▶ Treatment uptake among patients with MDR-TB infection.
	HIC	▶ Refugees.[64]	▶ Concern about medication adverse effects.[51] ▶ Country of origin.[40 99 166] ▶ Living in 'blended families'.[40] ▶ Moving away/transferred care before starting therapy.[83 95] ▶ Patient/caregiver refusal.[17 36 40 46 59 60 68 90 95 97 99]	▶ No analytic studies.	
7) Initiation of treatment → completion of treatment	LMIC	▶ Caregiver education.[56] ▶ Caregiver knowledge about TB infection and BCG.[81] ▶ Close relationship and close contact with TB index patients.[112] ▶ Personal health knowledge/beliefs.[56 81 136] ▶ Shorter therapy regimens.[22 106] ▶ Sociodemographic factors (Human Development Index).[30]	▶ Experience of or concerns about adverse medication effects.[56 102 107] ▶ Contact with adult TB contacts not receiving TB treatment.[30] ▶ Low income.[81] ▶ Medical contraindications (pregnancy, concurrent infectious disease).[93 107] ▶ Stigma.[56] ▶ Transportation-related factors (distance and cost).[81]	▶ Cash incentives.[107] ▶ DOPT.[34 35]	▶ Benefits and downsides of joint therapy management between specialists and primary care providers. ▶ Location of treatment/prescription (primary care clinics and health department clinics). ▶ Scalability or durability of effective pilot programmes, and translation to resource-limited settings. ▶ Use of novel adherence measurement strategies (eg, mHealth).
	HIC	▶ Female sex.[31] ▶ Family members undergoing TB testing.[68] ▶ Family support.[139] ▶ History of receiving care at the clinic.[82] ▶ Location of origin.[40 99 115 124] ▶ Psychological well-being and perceived mastery.[113 115 116] ▶ Refugees.[31] ▶ School achievement.[137 139] ▶ Shorter therapy regimens.[14 34 35 105 106 120 126 140 145 146] ▶ Treatment at health department and non-hospital clinics.[99 108] ▶ Younger age.[13 18 40 68 82 99 116 125 137 138] ▶ Other sociodemographic factors (eg, language at home, family composition and race/ethnicity).[40 51 83 113 115 116 138 143]	▶ Adverse home/family environment.[125] ▶ Delays in diagnostic steps.[40 82] ▶ Experience of or concerns about adverse medication effects.[17 19 31 35 36 82 83 108 109 118 120 121 125 126 132–135] ▶ Caregiver work conflicts.[135] ▶ Early discontinuation by physicians.[35 126] ▶ Forgetfulness.[51] ▶ Lack of cooperation from children.[51] ▶ Lack of patient/caregiver knowledge about TB infection.[135] ▶ Lack of caregiver understanding about treatment instructions.[126] ▶ Medical contraindications (pregnancy and concurrent infectious disease).[51 83 133] ▶ Movement away during treatment.[68 83 90 100 101 118 124] ▶ Patient/caregiver lack of knowledge about TB and treatment.[51] ▶ Prescriber type.[32] ▶ Time since immigration.[68] ▶ Younger age.[88]	▶ Adherence counselling/coaching*[31 139 142]. ▶ Contingency contracting for adolescents.*[116] ▶ DOPT*[13 14 17 85 88 90 94 118 125–127 129 130 132] ▶ Home nursing assessments/outreach.*[131] ▶ Life skills peer counselling.*[139] ▶ Multimodal treatment-tailoring to address convenience and social/structural barriers.[88 125] ▶ Provision of free medication.[119] ▶ Reward-based incentive programme.*[143] ▶ Self-esteem coaching.*[142] ▶ Telemedicine DOPT.[127]	

*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%[52] to 100%.[36 38 41 44]

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)[37] and 'parental avoidance' in Iran.[66] Low perceived risk also motivated caregivers to decline testing for their children.[49] Children also refused testing.[66 69] For example, among 5000 schoolchildren intended for testing in Iran, 220 'ran away from the team before they could be tested'.[66] 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 difficulty to contact or locate.[29 46 49 51 73–75] Additional patient/family-related factors that have been statistically associated with lack of testing included both older age[50 70] and younger age,[72] and presence of comorbidities.[66 75]

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.[61 74] Meanwhile, the setting of primary care delivery was found to affect testing uptake in the USA.[76]

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.[36 38 41 44–46 49–51 53–61 73 74 77] 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.[43]

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[39 65 68 69 78 79]; (2) non-school-based contact investigations[28 38 44 46 61 73]; and (3) primary care clinics.[70 71 76 80] Most studies demonstrated high rates of return (>90%) following TST placement,[28 36 38 40 44 46 61 65 81] although three studies conducted in primary care clinics in the USA documented lower return rates (58%–84%).[70 71 80]

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.[71] 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.[18] 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.[70] 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 (vs office-based clinic).[76]

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.[71] 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[28 36 38 41 46 81] and mass screenings at schools with at-risk students,[39 40 65 68 78 79] primary care clinics in the USA[70 82] and among asylum seekers in Denmark.[37] 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.[38 70] 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%),[28 36 38–41 46 51 78 79 82–85] although five studies documented rates <90%.[16 37 65 68 86] 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.[65]

Studies from high-income countries identified several barriers to evaluation completion. Family movement prevented completion of evaluation in two studies.[78 84] Movement included transitions of care to outside clinics, which disrupted documentation of evaluation completion, as in a study of international adoptees in the USA.[84] 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.[78] 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.[40]

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.[28] 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.[16 28 33 36–41 43 46 51 53 54 56 57 59 60 65 67 81–83 87–100] 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.[101] 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[37 87] and presumed false-positive tests in the setting of prior BCG vaccination.[94]

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[102] and elevated transaminases and medical instability in exposed neonates in South Korea.[38] 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'.[103] 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.[103] 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[95] to 100% in several studies.[28 37–39 41 46 51 53 54 74 87–89 92 94 96 100]

In both high-income countries and LMICs, patient or caregiver refusal was a major barrier to treatment initiation.[17 33 36 40 46 59 60 68 81 90 93 95 97 99 102 104] Several studies have examined reasons for treatment acceptance and refusal. Patient and caregiver concerns about medication adverse effects were a common cause of treatment refusal.[51 104] 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.[104]

Patient demographic characteristics have been linked to treatment refusal in high-income countries.[40 64 99] 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)).[40] 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.[99] 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.[64]

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.[83 95] 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,[105] 3 months of rifampin and isoniazid[105 106] and 3 months of isoniazid and rifapentine via directly observed preventive treatment (DOPT) for paediatric patients over 2 years old[105] 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.[22]

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.[107] 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.[36 108 109]

Several studies from both high-income countries[32 90 99 110 111] and LMICs[29 30 112] 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[14 16 51 94 102 113–117] or TB/infectious diseases/chest clinics.[31 40 83 90 111 118–126] DOPT was also frequently employed and universally used when patients were prescribed isoniazid plus rifapentine.[35 67 127 128] Apart from treatment-specific use of DOPT, other indications for DOPT were inconsistent across studies, with some reserving DOPT for young patients[118] or those perceived to be at high risk for, or have proven, non-adherence.[94 125 129]

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%).[85] 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 7.2 9(95% CI 5.7 to 23.6)).[90] 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.[83 95 108 130] 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 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.[131] 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.[17 19 31 35 36 56 82 83 102 107–109 118 120 121 125 126 132–135] Likewise, medical contraindications to treatment that occurred during treatment courses, such as pregnancy or intercurrent non-TB infections, occasionally prompted discontinuation.[51 83 93 107 133] In studies from LMIC, additional factors associated with treatment completion included caregiver education[56] and knowledge about TB infection,[81] personal health knowledge and beliefs,[56 81 136] lack of stigma[56] and close relationships with TB contacts.[112]

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[13 18 40 68 82 99 116 125 137 138] and older age,[88] female sex,[31] race/ethnicity,[116 138] family composition[40 51 113] and origin,[40 99 115 124] supportive family and home environments[125 139] and school achievement.[137 139] Meanwhile, patient/family movement away from catchment areas could interrupt treatment.[68 83 90 100 101 118 124] 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.[51 126 135]

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.[135] 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.[116 139 142] 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.[116] 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).[113 115 116] Another trial, based on the Behavioral 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 incentives[107] 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[144] 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 34 35 105 106 120 126 140 145 146] 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[32]; potential for mobile health technologies (mHealth) to optimise adherence[127]; 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 likely[140] or less likely[32] 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 factors[155] 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 old[156]; 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 procedures[48] and multilevel community interventions.[159]

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.[115 116 142 143] 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,[25 160] 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,[23] 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.[27] 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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