

Tuberculosis research principles and priorities in children and adolescents: an international consensus statement



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Each year, an estimated 1·9 million children (aged 0–9 years) and adolescents (aged 10–19 years) develop tuberculosis disease. Tuberculosis ranks among the top ten causes of death in children younger than 5 years. The primary driver of tuberculosis-related mortality in children and young adolescents is the failure to detect and treat the disease; more than 95% of tuberculosis deaths occur in children who were never initiated on tuberculosis treatment. To increase the quantity and quality of tuberculosis research required to strengthen clinical care and public health practice, the Child and Adolescent TB Working Group and its Secretariat at the WHO led a modified Delphi consensus process to generate core research principles and priorities along each step of the tuberculosis care cascade. An 11-member writing group drafted an initial list of principles and priorities, which were ranked by members of the consensus panel in each Delphi round. Principles and priorities that did not meet the consensus threshold were modified based on written qualitative feedback from the consensus panel and one-time input from other members of the Child and Adolescent TB Working Group at the group's 2024 annual meeting. Eight research principles and 21 research priorities emerged from two Delphi rounds. The research priorities have strong potential for translation into interventions, particularly in relation to diagnostics, shorter regimens, and tuberculous meningitis. With recently reduced tuberculosis research funding, these principles and priorities will focus research efforts to maximise clinical and public health impact.

Introduction

In 2024, an estimated 843 000 children (aged 0–9 years) and 1 065 000 adolescents (aged 10–19 years) developed tuberculosis disease (appendix pp 6–7).¹ Children and adolescents have unique needs and vulnerabilities. Children younger than 2 years are at greatest risk of progressing from *Mycobacterium tuberculosis* infection to severe forms of tuberculosis disease.² This risk decreases later in childhood but rises precipitously during adolescence, with a pronounced shift towards adult-type disease phenotypes.³ Globally, children and young adolescents (<15 years) account for an estimated 14% of all tuberculosis deaths, despite accounting for only 11% of incident tuberculosis and having high treatment success rates: 92% for drug-susceptible tuberculosis and 80% for multidrug-resistant or rifampicin-resistant tuberculosis.^{1,4}

The primary driver of tuberculosis-related mortality in children and young adolescents is the inability to detect and treat tuberculosis disease; more than 95% of tuberculosis deaths occur in those who were never initiated on tuberculosis treatment, almost always because they were not diagnosed.⁵ Tuberculosis diagnosis is less challenging in older adolescents (aged 15–19 years), in whom respiratory samples are more easily obtained and *M tuberculosis* is more readily detectable. Nonetheless, tuberculosis ranks among the top three causes of death among older adolescents,⁶ with tuberculosis-related mortality strongly influenced by models of service delivery that do not meet their needs, as evidenced by high loss to follow-up rates relative to other age groups.^{7–9}

Intensified research and innovation are key components of WHO's *End TB Strategy*,^{10,11} but research focused on children and adolescents is underfunded. Research funding trends from 2005 to 2023 show that less than

10% of total funding for tuberculosis research was allocated to studies involving children and adolescents.¹² Most new tuberculosis diagnostics are developed for, and

Key messages

- Given the current burden of tuberculosis morbidity and mortality in children and adolescents, and shrinking resources to address their needs, the Child and Adolescent TB Working Group led an international consensus process to identify key research principles and priorities to guide future tuberculosis research focus and investment.
- Principles were defined as fundamental facts and assumptions that should motivate and guide tuberculosis research. The eight principles that emerged from the consensus process highlighted the need for: greater investment in the development of better tools for tuberculosis detection, treatment, and prevention; implementation research to facilitate innovation uptake and access; and a focus on reducing tuberculosis-associated impairment and disability.
- Priorities were defined as specific knowledge gaps along the tuberculosis care cascade that were considered most important or urgent to reduce tuberculosis-related morbidity and mortality. Key research priorities include tuberculosis screening and diagnosis, the need for shorter and safer regimens for both tuberculosis prevention and disease treatment, and a special focus on tuberculous meningitis as the most devastating tuberculosis disease manifestation.
- The diversity and representativeness of the expert panel, as well as the inclusion of people with lived experience, ensured the consideration of patient perspectives and challenges in high tuberculosis incidence settings with scarce resources.

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See Online for appendix

For more on the approval of new tuberculosis drugs see <https://www.cheetfortb.org/>

tested in, adults; evaluations in children and adolescents are often delayed, if they are done at all.¹³ Similarly, tuberculosis treatment trials in children and young adolescents lag far behind the same studies in adults, leading to an average 10-year gap (range 8–13 years) between the approval of new tuberculosis drugs for adults and children.¹⁴ A 2025 systematic review on the respiratory sequelae in people with pulmonary tuberculosis found that of 119 studies meeting selection criteria, only five (4%) reported disaggregated data for children or adolescents.¹⁵

The historical neglect of children and adolescents in tuberculosis research stems from multiple factors. Firstly, children have been deprioritised in tuberculosis control efforts because they are generally less infectious than adult patients and contribute little to *M tuberculosis* transmission within communities. Adolescents, however, tend to develop infectious adult-type tuberculosis, while having unique health-care needs to which services need to adapt.¹⁶ Secondly, studies commonly use microbiological confirmation of *M tuberculosis* as an inclusion criterion, but this criterion leads to the exclusion of most children, given the difficulty of specimen collection and the poor sensitivity of currently available diagnostic tests in people with paucibacillary disease.¹⁷ In addition, there are legal complexities related to informed consent for minors and the perception that children and adolescents represent vulnerable groups in need of protection from the potential harms of research. Many ethics committees do not have the expertise to guide the conduct of responsible paediatric research, and investigators often do not wish to take on the additional requirements of enrolling minors. However, more harm is caused by study exclusion and the resulting lack of data to inform policy and guide management.¹⁸

To increase the quantity and quality of tuberculosis research required to improve clinical care and strengthen public health practice related to tuberculosis in children

and adolescents, the Child and Adolescent TB Working Group aimed to generate international consensus around key research principles and priorities to guide future tuberculosis research focus and investment. Following reductions in tuberculosis care and research funding, scarce resources need to be focused on areas of highest priority and anticipated impact. This consensus process aligns with the *Roadmap Towards Ending TB in Children and Adolescents*, which highlights that tuberculosis research in children and adolescents is one of ten key actions needed to address persistent gaps in tuberculosis prevention and care.⁴ The consensus process also builds upon previously published research priorities, many of which used less rigorous methods.^{4,13,18–25}

Methods

Participants

This consensus process followed modified Delphi methodology with three groups of participants.²⁶ First, 11 international experts in child and adolescent tuberculosis (listed coauthors) served as the writing group. This group included staff from WHO's Department of HIV, Tuberculosis, Hepatitis, and Sexually Transmitted Infections, who served as the Secretariat of the Child and Adolescent TB Working Group (comprised of approximately 500 members) and its core team.²⁷ Second, the core team of the Child and Adolescent TB Working Group; researchers and clinicians from high and low tuberculosis incidence countries; and representatives of civil society organisations, national tuberculosis programmes, and international funding agencies were invited to participate in the Delphi rounds as members of the consensus panel. Finally, all members of the Child and Adolescent TB Working Group, which includes tuberculosis survivors and their families, were invited to provide feedback at the annual hybrid meeting in Bali, Indonesia, on Nov 11, 2024.

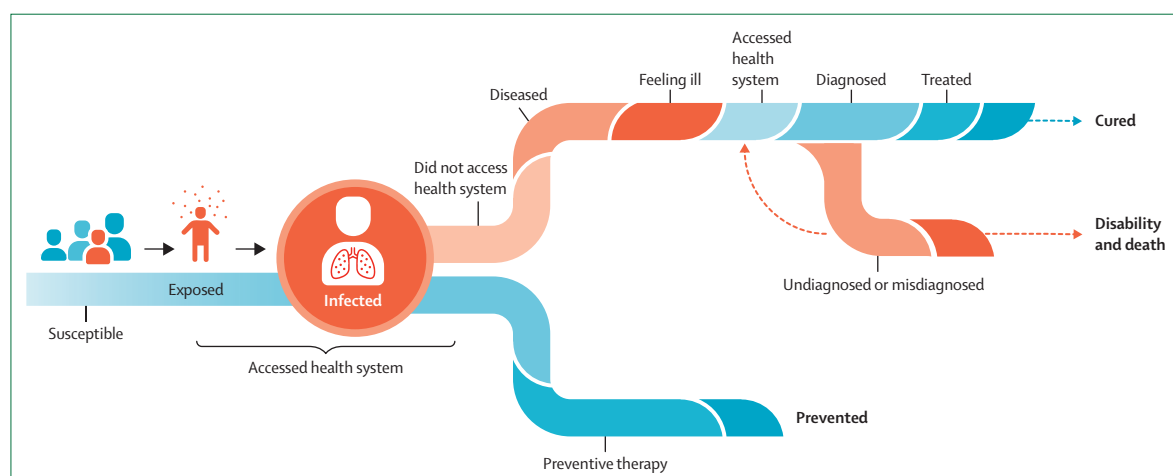


Figure 1: Tuberculosis care cascade

Reproduced from WHO.⁴ Research priorities were considered across the full cascade of care. Children can also progress to disability even after treatment and cure.

Consensus process

Principles were defined as fundamental facts and assumptions that should motivate and guide tuberculosis research in children and adolescents. Priorities were defined as specific knowledge gaps along the tuberculosis care cascade (figure 1) that are most important or urgent to reduce tuberculosis-related morbidity and mortality in children and adolescents.

The writing group drafted a preliminary list of ten research principles and 37 priorities. First, the group compiled all research priorities listed in four reports published by the WHO or the Child and Adolescent TB Working Group between 2018 and 2024.^{4,20,23,24} Each priority was categorised into the step of the tuberculosis care cascade to which it corresponded (appendix pp 8–13). Drawing on these categorised priorities, three authors (MPS, SSC, and BJM) drafted initial research principles. These principles and priorities were circulated among the writing group for edits and comments and then finalised for the first Delphi round after two hour-long online discussions.

Delphi rounds were done with Research Electronic Data Capture (known as REDCap) hosted at Brown University Health (Providence, RI, USA). To maximise participation, three reminders were sent out for each Delphi round. People who did not participate in a round were excluded from subsequent rounds.

In each Delphi round, members of the writing team and the consensus panel ranked principles with a five-point Likert scale: 1 was strongly disagree, 2 was disagree, 3 was neutral, 4 was agree, and 5 was strongly agree. Adapting the approach used by Velayutham and colleagues,¹⁹ priorities were scored with the Likert scale according to five criteria: (1) novelty—ie, the answer to this research question is not currently known or able to be extrapolated from currently available evidence; (2) answerability—ie, it is feasible to collect the data needed to answer this research question and possible to do so in an ethical way; (3) potential for translation—ie, the answer to this research question will lead to an intervention; (4) potential impact on disease burden or outcome—ie, the answer to this research question will lead to the reduction of tuberculosis burden, morbidity, or mortality among children and adolescents; and (5) equity—ie, the findings from this research question will reduce disparities in tuberculosis burden or outcome across settings and groups of children and adolescents. The five scores were averaged into an overall score; their identical weights reflected the equal importance attributed to each criterion by the writing group. In each round, participants were invited to provide written qualitative feedback by suggesting new principles and priorities or revisions to existing ones.

Additional qualitative feedback was solicited after the first Delphi round from all members of the Child and Adolescent TB Working Group at the group's 2024 annual meeting, which took place before the World Lung

Health Conference in Bali, Indonesia, with an option for online participation. The meeting was attended by 164 people, including tuberculosis survivors and their families. Draft principles and priorities, their rankings, and summarised qualitative feedback for each were shared with all attendees. This timepoint was the only instance when rankings and qualitative feedback were shared with participants outside the writing group. Tuberculosis survivors and their families, along with the other attendees, were engaged in discussions and participated in live polls with Slido (Cisco Systems, London, UK).

After each Delphi round, the writing group accepted principles and priorities that met a-priori consensus thresholds: for principles, 85% or more of scores must be 4 or above, and for priorities, 80% or more of overall scores must be 3·5 or above. However, after the first Delphi round, if a principle or priority met the consensus threshold but several participants (from the consensus panel or the Child and Adolescent TB Working Group meeting) raised the same objections or suggestions for improvement, then it was discarded or revised by the writing group. After the second Delphi round, the writing group accepted all principles and priorities that met consensus thresholds. Data were analysed with R.

Results

Consensus was reached after two Delphi rounds (figure 2). The first round began on Oct 25, 2024, and

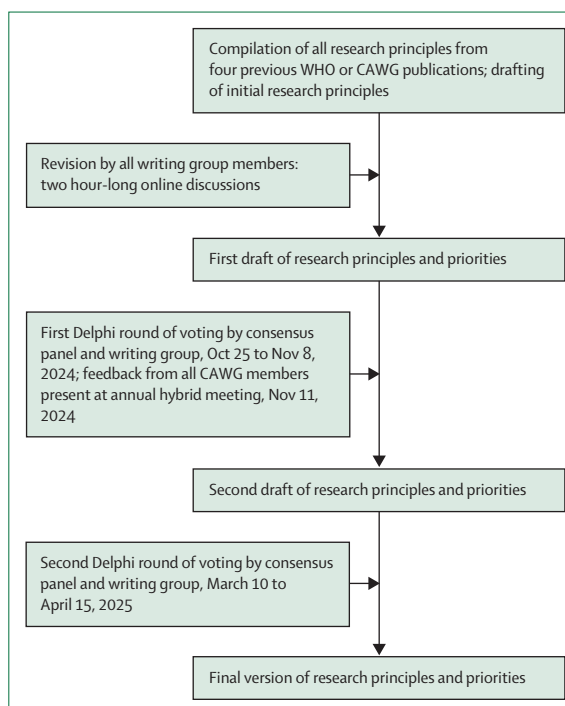


Figure 2: Modified Delphi consensus process
CAWG=Child and Adolescent TB Working Group.

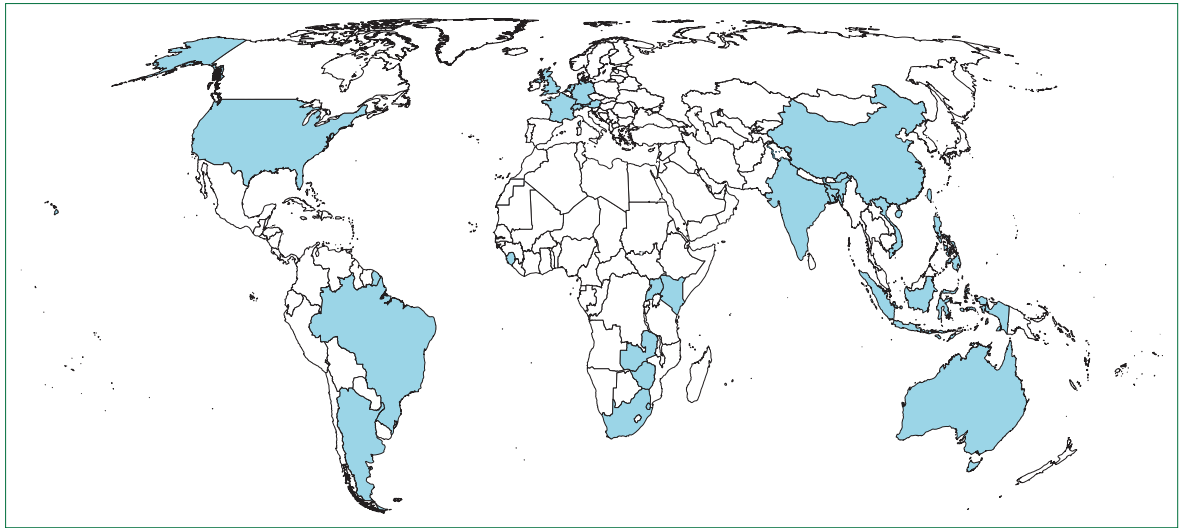


Figure 3: Countries represented by Delphi consensus participants

The blue shading highlights the locations of the institutional affiliations for the members of the writing team and consensus panel.

concluded on Nov 8, 2024. The Child and Adolescent TB Working Group hybrid meeting, during which additional feedback was solicited, was held on Nov 11, 2024. The second Delphi round began on March 10, 2025, and concluded on April 15, 2025.

11 writing group members and 45 (88%) of 51 people invited to serve on the consensus panel participated in the first Delphi round (key characteristics of participants are in the appendix [p 14]). These 56 participants represented 23 countries (figure 3). Due to changes to their institutional affiliation or their institution's policies, one writing team member and five consensus panel members were unable to participate in the second Delphi round. Four additional consensus panel members did not complete the second Delphi round, leaving a total of 46 participants.

Research principles

Of the ten research principles presented for the first Delphi round, eight met the consensus threshold. Based on written qualitative feedback from the consensus panel and feedback from the Child and Adolescent TB Working Group meeting, the writing group discarded one principle and revised the others (appendix pp 15–18). No new principles were added. The nine revised principles met the consensus threshold in the second Delphi round. However, one of them was not strictly classified as research and thus not included in the final set. This candidate principle, which achieved 89% consensus, stated that tuberculosis notification data should be reported from all sites where children and adolescents seek tuberculosis care. Ideally, these data should include disease type (pulmonary, extrapulmonary—specifying tuberculous meningitis—or disseminated disease), key risk factors (HIV status, nutritional status, pregnancy), and treatment outcomes disaggregated by 5-year age

bands (0–4, 5–9, 10–14, 15–19 years). Programmatic indicators of contact investigation, tuberculosis preventive treatment (TPT) initiation, and TPT completion should also be reported.

We have summarised the final eight research principles and the rationale for each (table 1).^{1,5,6,28,29} Reducing high tuberculosis-related mortality in children and adolescents requires greater investment into the research and development of tools and treatment to improve early tuberculosis detection, treatment, and prevention (principle 1). Implementation research is needed to improve children's and adolescents' access to effective tuberculosis interventions, particularly in high tuberculosis incidence settings with limited resources (principle 2). Limiting tuberculosis-associated impairment and disability among children and adolescents requires research to better understand the burden and pathogenesis of long-term sequelae, with the eventual goal of developing effective strategies for prevention, care, and rehabilitation (principle 3). Several participants emphasised the need for this research to differentiate children (0–9 years) and adolescents (10–19 years) from adults (≥ 20 years), given differences in pathogenesis and the clinical spectrum of disease.⁴

Research should address areas in which evidence from adult studies cannot be readily extrapolated to children and adolescents (principle 4; table 1). Examples included host immune responses that mature over time; unique case finding and diagnostic challenges; and age-related variation in drug dosing, distribution, preferred formulations, safety, and tolerability. Participants recognised that adolescents do not fit neatly into paediatric or adult categories. Their clinical presentation and ability to produce sputum, and the sensitivity of microbiological assays and the pharmacokinetic and dynamic profiles of drugs

	Rationale	% with score ≥ 4 *
(1) Reducing high tuberculosis-related mortality in children and adolescents requires greater investment into the research and development of tools and treatment to improve early tuberculosis detection, treatment, and prevention.	Despite being preventable and treatable, tuberculosis kills an estimated 300 000 children and adolescents each year. ¹⁶ Most of these deaths occur in individuals who did not access diagnosis, treatment, or prevention services. ^{5,28}	96%
(2) Implementation research is needed to improve children and adolescents' access to effective tuberculosis interventions, particularly in high tuberculosis incidence settings with limited resources.	Children and adolescents, especially those living in resource-limited settings, are often unable to benefit from existing tools and treatment regimens given limited access in areas of greatest need.	89%
(3) Limiting post-tuberculosis disability among children and adolescents requires research to better understand the burden and pathogenesis of long-term sequelae, with the eventual goal of developing effective strategies for prevention, care, and rehabilitation.	Tuberculosis can lead to long-term sequelae following successful treatment. An estimated 1.9 million children and adolescents develop tuberculosis each year, ^{1,29} and given their many remaining years of life, tuberculosis will be responsible for a substantial global burden of long-term disability.	91%
(4) Research should address areas in which evidence from adult studies cannot be readily extrapolated to children and adolescents, given their unique needs and vulnerabilities.	Children and adolescents have unique tuberculosis vulnerabilities and needs, which might preclude extrapolation of findings from adult studies. Examples of these areas include host immune response; screening and diagnosis; drug pharmacokinetics, dosing, formulation, tolerability and safety; and psychosocial impacts.	96%
(5) Adolescents should be considered for inclusion in studies primarily focused on adults and children, with reporting of age-disaggregated findings for younger (10–14 years) and older adolescents (15–19 years).	Adolescents do not fit neatly into either paediatric or adult age groups and are often neglected in tuberculosis research, whereas variable age cutoffs complicate data collation and interpretation.	87%
(6) Both the feasibility and acceptability of proposed interventions for children, adolescents, their families, and health-care providers require evaluation to facilitate effective policy translation and uptake.	Feasibility and acceptability are key to inform local implementation and uptake of policy, including for WHO recommendations of interventions with compelling evidence of effectiveness and safety.	93%
(7) Children and adolescents have a right to benefit from research and should not be excluded from research based on perceived vulnerability or recruitment difficulties.	Tuberculosis studies should include—in a timely manner—participants that reflect the full spectrum of affected communities. The unwarranted exclusion of children and adolescents causes harm by limiting the evidence informing policy and practice.	91%
(8) In high tuberculosis incidence settings, it is important to build capacity and supportive infrastructure for high-quality, collaborative research that includes children, adolescents, and their families.	To inform global policy and practice we need studies from diverse high tuberculosis incidence settings. These settings have limited research capacity and infrastructure, which is more pronounced for research in children and adolescents.	96%

*A-priori consensus threshold: more than 85% of participants gave a score between 4 and 5.

Table 1: Consensus principles for research about tuberculosis in children and adolescents

resemble those of adults. However, adolescents have specific needs with respect to tuberculosis care and engagement, some of which overlap with the needs of children and some that do not. Participants reached consensus that adolescents should be considered for inclusion in studies primarily focused on adults and children, with reporting of age-disaggregated findings for younger (aged 10–14 years) and older adolescents (aged 15–19 years; principle 5). Several participants advocated for studies that exclusively enrol adolescents to focus on their distinct needs.

Both the feasibility and acceptability of proposed interventions for children, adolescents, their families, and health-care providers require evaluation to facilitate effective policy translation and uptake (principle 6; table 1). Research ethics committees classify children and adolescents as vulnerable populations, which discourages their inclusion in research. Children and adolescents have a right to benefit from research and should not be excluded based on perceived vulnerability or recruitment difficulties (principle 7). The staggered age de-escalation approach that is often adopted by manufacturers of new tuberculosis drugs is not a regulatory requirement and

might lead to unnecessary delays in paediatric treatment access. In high tuberculosis incidence settings, it is important to build capacity and supportive infrastructure for high-quality, collaborative research that includes children, adolescents, and their families (principle 8). Participants emphasised that studies on tuberculosis in children and adolescents are needed from diverse high tuberculosis incidence settings, which is hampered by limited research capacity and infrastructure.

Research priorities

Of 35 research priorities presented for the first Delphi round, 11 were accepted, 11 were discarded, and 13 were revised. One new priority (Evaluate the feasibility, acceptability, and effectiveness of community-wide active tuberculosis case finding among adolescents in settings with high tuberculosis transmission) was added based on feedback from the consensus panel. Of the 12 research priorities presented for the second Delphi round, eight were accepted, four were discarded, and none were revised (appendix pp 19–46).

The final 21 consensus research priorities identified across the tuberculosis care cascade are summarised in

	Overall score $\geq 3.5^*$ (%)
Tuberculosis exposure and infection	
Quantify the peripartum (in pregnancy and ≤ 6 months after giving birth) tuberculosis disease and transmission risk in high tuberculosis incidence setting, as well as the impact on infant health.	96%
Tuberculosis disease prevention	
Develop new vaccines with greater efficacy, effectiveness, and longer-term protection for preventing tuberculosis disease (all forms) in children and adolescents, irrespective of HIV status.	100%
Develop shorter and safer (more acceptable) TPT regimens for drug-susceptible and drug-resistant tuberculosis.	98%
Evaluate health-care delivery models that optimise uptake and completion of TPT for children, adolescents, and their families.	94%
Tuberculosis disease screening	
Find biomarkers indicating progression from <i>Mycobacterium tuberculosis</i> infection to tuberculosis disease in children and adolescents.	93%
Identify strategies to optimise the diagnostic yield of tuberculosis contact investigation.	90%
Determine the optimal approaches for tuberculosis disease screening (frequency and tools) among children and adolescents living with HIV, severe malnutrition and/or other forms of immunosuppression.	100%
Evaluate the feasibility, acceptability, and effectiveness of community-wide active tuberculosis case finding among adolescents in settings with high tuberculosis transmission.	88%
Tuberculosis disease diagnosis	
Develop point-of-care tests for the diagnosis of tuberculosis disease, including in children and adolescents living with HIV and/or severe malnutrition. Assess diagnostic accuracy, yield, feasibility, and acceptability.	96%
Timely evaluation of all new diagnostic assays in children and adolescents, including performance on all sample types currently recommended by the WHO.	96%
Evaluate computer-aided chest x-rays interpretation in children (<10 years) and young adolescents (10–14 years), including those living with HIV.	96%
Assess and improve the diagnostic performance, feasibility, and acceptability of integrated treatment decision algorithms, including in children and adolescents who are undernourished and/or living with HIV.	93%
Develop and validate algorithms to diagnose extrapulmonary tuberculosis in children and adolescents, including those living with HIV and/or severe malnutrition.	84%
Develop and validate non-invasive approaches to collect respiratory specimens.	86%
Tuberculosis disease treatment (drug-susceptible and drug-resistant)	
Evaluate novel shorter and/or safer treatment regimens for drug-susceptible and drug-resistant tuberculosis in children and adolescents.	98%
Evaluate the feasibility and acceptability of implementing existing shorter regimens, including the ability to diagnose non-severe disease in settings with limited access and capacity to interpret chest x-rays.	94%
Optimise new and existing drug formulations and dosing for treating drug-resistant tuberculosis and extrapulmonary tuberculosis in children.	89%
Evaluate the pharmacokinetics, dosing, efficacy, and safety of regimens for tuberculous meningitis, including long-term outcomes or sequelae, in children and adolescents.	95%
Post-treatment sequelae	
Identify the risk factors and pathophysiology of tuberculosis-associated chronic respiratory disability in children and adolescents, with the aim of developing preventive interventions.	87%
Identify and evaluate adjuvant therapies given during treatment for tuberculous meningitis to prevent long-term neurological sequelae in children and adolescents.	92%
Approaches across the care cascade	
Develop and evaluate approaches to optimise engagement with tuberculosis care among adolescents, children, and their families. This work should include individuals at risk of adverse outcomes, including those who are living with HIV or severe malnutrition, are pregnant, use substances, and/or are unhoused or living independently.	88%
TPT=tuberculosis preventive treatment. *A-priori consensus threshold: more than 80% of participants gave an overall mean score of 3.5–5.	

Table 2: Consensus priorities for research along the tuberculosis care cascade in children and adolescents

table 2 and the appendix (pp 47–48). Given the large number of research priorities, those with an overall score of 3.5 or above from 90% or more of participants were labelled highly ranked to indicate broad consensus about their importance. 15 priorities were highly ranked (overall score ≥ 3.5 from $\geq 90\%$ of participants). For tuberculosis exposure, the only research priority that reached consensus centred on improving understanding of tuberculosis disease and transmission risk during pregnancy and the

postpartum period, as well as its impact on the health of infants. All three priorities targeting the prevention of progression from *M tuberculosis* infection to tuberculosis disease were highly ranked; these priorities called for the development of effective vaccines, shorter and more acceptable TPT regimens, and models of health-care delivery to optimise TPT uptake and completion. Given that several well tolerated TPT regimens exist for drug-susceptible *M tuberculosis* infection, some participants

prioritised regimens targeting drug-resistant infection, or regimens effective for both drug-susceptible and drug-resistant infection.

In the tuberculosis disease screening step of the care cascade, participants highly ranked priorities that addressed the identification of biomarkers that predict tuberculosis disease progression risk; improved tuberculosis contact investigation; and the development of optimised approaches (including frequency and tools) for tuberculosis screening among children living with HIV, severe malnutrition, or other forms of immunosuppression. Evaluating the feasibility, acceptability, and effectiveness of community-wide active tuberculosis case finding among adolescents in settings with high tuberculosis transmission reached consensus but was not highly ranked. This priority focused on adolescents because diagnosis with existing tools (chest x-ray or a WHO-recommended rapid molecular diagnostic test) is more straightforward in this age group, relative to children. Some participants objected to this priority not including children, whereas others stated that data obtained from studies in adults can be applied to adolescents—and adolescents should ideally be included in adult active case finding studies.

Four of six research priorities addressing tuberculosis disease diagnosis were highly ranked, including the development of biomarker-based point-of-care tests, timely evaluation of all new diagnostic tests in children and adolescents, and assessment of computer-aided chest x-ray reading (table 2). In the absence of readily available tests with high diagnostic accuracy, improvement of the diagnostic performance, feasibility, and acceptability of integrated treatment decision algorithms remains essential and was also highly ranked. The development and validation of algorithms to diagnose extrapulmonary tuberculosis and non-invasive approaches to collect respiratory samples were less strongly endorsed.

Highly ranked priorities related to tuberculosis disease treatment focused on shorter and safer regimens for both drug-susceptible and drug-resistant tuberculosis, and for the feasibility of implementing existing shorter regimens in settings with less access to chest x-rays and the ability to interpret them. A specific focus on tuberculous meningitis was justified by poor treatment outcomes, with high mortality and frequent severe neurological sequelae in survivors. Two priorities included not only traditional treatment outcomes (ie, cure, death), but also assessment of longer-term impairment and disability. The inclusion of person-centred outcomes (ie, outcomes important to children and adolescents affected by tuberculosis and their families) in TPT or tuberculosis treatment trials was noted as an important methodological consideration but was not considered a research priority. A priority on the optimisation of dosing guidance and formulations of new and existing drugs for paediatric drug-resistant and extrapulmonary tuberculosis was less highly ranked.

Participants commented that a lot of this work has been done, although it remains important when new drugs and regimens are being developed. For tuberculous meningitis, participants noted that dose optimisation alone might not improve outcomes, if done without consideration of host-directed therapy.

In the post-treatment step of the tuberculosis care cascade, the evaluation of adjuvant therapies (during tuberculosis treatment) to prevent long-term neurological sequelae in children and adolescents with tuberculous meningitis was highly ranked. Understanding the risk factors and pathophysiology of tuberculosis-associated respiratory disability—with the eventual goal of developing interventions—also reached consensus but was not highly ranked. Notably, a research priority that did not reach consensus called for the refinement of case definitions of tuberculosis-associated respiratory impairment and disability and the identification of feasible, reliable, and valid assessment approaches in young children. Participants acknowledged that standardised definitions and methods were needed to facilitate and advance the necessary research, but they did not consider it to be a research priority per se because it would lead to neither an intervention nor a reduction in tuberculosis burden, morbidity, or mortality.

The final research priority that reached consensus spanned multiple steps of the tuberculosis care cascade (table 2). Although participants acknowledged the importance of engagement in tuberculosis care, especially for adolescents, they considered the current formulation of the priority to be too vague and wordy: “Develop and evaluate approaches to optimise engagement with tuberculosis care among adolescents, children, and their families. This work should include individuals at risk of adverse outcomes, including those who are living with HIV or severe malnutrition, are pregnant, use substances, and/or are unhoused or living independently.” Participants acknowledged the need to address the social determinants of health and to improve service delivery, but no specific research priority was formulated.

Discussion

The consensus process identified a comprehensive but focused set of key research principles and priorities. Highly ranked research priorities addressed important and answerable questions, with strong potential for translation into interventions that will reduce tuberculosis-related morbidity and mortality in children and adolescents. With recent reductions to tuberculosis research funding, scarce resources should be focused on areas where the greatest impact is likely to be gained.³⁰

Three priority areas stood out. Firstly, a strong focus on tuberculosis screening and diagnosis reflects persistent gaps in tuberculosis prevention and treatment

access, especially for vulnerable young children in high tuberculosis incidence settings where most tuberculosis deaths occur.⁴ Although innovative new tools are needed, participants emphasised that much of the case detection gap stems from structural health-care barriers and poor implementation of existing tools.³¹ For this reason, operational research related to tuberculosis prevention and case finding was included among the highly ranked research priorities. The ongoing development and eventual roll-out of diagnostic innovations, such as host response-based biomarkers and computer-aided chest x-ray interpretation, can help address these barriers. A consensus framework from 2024 promotes the early inclusion of children and adolescents in the design and evaluation of these new tools.¹³

The need for shorter and safer regimens—for both tuberculosis prevention and disease treatment—stood out as the second key research area. Finding shorter and more acceptable regimens for TPT and drug-resistant tuberculosis is important since shorter regimens are associated with higher completion rates.^{32–34} Similarly, adherence among adolescents to treatment for rifampicin-susceptible tuberculosis disease decreases after the fourth month of treatment.³⁵ Shorter regimens also reduce financial and logistical burdens on families. The WHO recommended 4-month regimen for the treatment of non-severe, drug-susceptible tuberculosis in children and adolescents aged 15 years or younger represents an important advance.²³ However, implementation has been challenging in high tuberculosis incidence settings where paediatric chest x-rays, an essential tool for assessing eligibility, are not readily available. This challenge shows the need for studies that evaluate the feasibility and acceptability of new treatment approaches in areas of greatest need. The Special Programme for Research and Training in Tropical Diseases is currently developing an operational research package to assess whether clinical criteria can be used to assess regimen eligibility in resource-limited settings.

Search strategy and selection criteria

Draft research principles and priorities were directly informed by reports published by WHO or the Child and Adolescent TB Working Group between Jan 1, 2015, and Aug 31, 2024. These reports were provided by the Child and Adolescent TB Working Group's Secretariat, who is based at WHO. Throughout the consensus process, the writing group also reviewed English-language consensus statements related to paediatric tuberculosis, which were identified through PubMed with the publication date range of Jan 1, 2015, to Aug 31, 2024 and this query: (consensus[Title/Abstract]) AND (tuberculosis[Title/Abstract]) AND (child[Title/Abstract] OR adolescent[Title/Abstract]). Members of the writing group also suggested key references to support the findings of this consensus process.

Finally, research priorities related to tuberculous meningitis, the most severe and deadly tuberculosis disease manifestation, were both highly ranked and strongly endorsed in the written qualitative feedback from the consensus panel. An estimated 24 000 children and young adolescents (<15 years) developed tuberculous meningitis in 2019, of whom 16 100 died (67%) and another 5550 (70% of survivors) were left with neurological sequelae.³⁶ Despite these appalling outcomes, there is a dearth of tuberculous meningitis trials, not only of antituberculosis regimens, but also of host-directed therapies aimed at moderating the inflammatory response that underlies the main pathology.^{21,37,38} The Tuberculous Meningitis International Research Consortium previously published a detailed summary of research gaps and priorities related to tuberculous meningitis.²¹ A major challenge for tuberculous meningitis studies is the small number of cases diagnosed at each centre, rendering it difficult to reach a sufficient sample size within the timeframe of most research grants. Even higher-volume centres face recruitment obstacles with late presentation and delayed referrals, as well as logistical and emotional (on the part of family members) difficulties in enrolling sick patients.³⁹ Effective multicentre collaborations are crucial to advance this important area of research.

Strengths of this modified Delphi process include the diversity and representativeness of the people involved in the consensus process. Gathering input from tuberculosis survivors and their families at the Child and Adolescent TB Working Group meeting ensured that their perspectives were considered. The fact that the initial research principles and priorities were drafted by a small writing group is a limitation, but was ameliorated by the open invitation for additional research principles and priorities to be suggested during each Delphi round and at the Child and Adolescent TB Working Group meeting. Most writing group and consensus panel members were based in high-income countries, and certain subregions of the world—including eastern Europe, central Asia, and the Middle East—were under-represented. Notably, these consensus principles and priorities present a broad overview across the full tuberculosis care cascade, thus limiting highly detailed considerations. As such, this Health Policy complements other resources, such as research priorities identified during Guideline Development Group processes and statements that focus on specific areas of tuberculosis care.^{13,21}

In conclusion, we used a rigorous international consensus process to identify key principles and priorities to guide tuberculosis research in children and adolescents with maximal impact. Continued and increased investments in tuberculosis research are crucial to drive the development of more effective and accessible prevention, diagnosis, treatment, and models of care in diverse settings. Ultimately, research outcomes

require effective and scaled translation into everyday practice to reduce the large and disproportionate burden of tuberculosis related disease, disability, and death in children and adolescents.

Contributors

All authors conceptualised the study. MPS and SSC collected, had access to, and verified the data. SSC analysed the data. MPS and SSC drafted the manuscript. All authors and all named members of consensus panel voted in the Delphi rounds, critically reviewed the manuscript, approved the final version for submission, and accept responsibility for submission for publication.

Declaration of interests

We declare no competing interests.

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