The inclusion of children and adolescents in tuberculosis diagnostic development and evaluation—a consensus statement

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The diagnosis of paediatric tuberculosis remains a challenge due to the non-specificity of symptoms and the paucibacillary nature of tuberculosis in children. However, in the development of new tuberculosis diagnostics, the unique needs of children and adolescents are rarely considered in the design process, with delays in evaluation and approval. No clear guidance is available on when and how to include children and adolescents in tuberculosis diagnostic development and evaluation. To address this gap, we conducted a Delphi consensus process with 42 stakeholders, including one qualitative and two quantitative rounds. Consensus was achieved on 20 statements, with agreement that the needs and perspectives of children, adolescents, and their caregivers should be incorporated throughout diagnostic design and evaluation. Opportunities exist for the early use of well characterised samples and prospective enrolment of children and adolescents in tuberculosis diagnostic evaluation, with consideration of the type of test, expected benefit, and potential risks. Pathogen-based tests might be initially optimised and assessed in adults and adolescents, but parallel evaluation in children is needed for host-based tests. Late-stage evaluation and implementation studies should examine combination testing and integration into clinical algorithms. The statements support collaboration between developers, researchers, regulators, and users to widen and accelerate the diagnostic pipeline for paediatric tuberculosis.

Introduction

Tuberculosis remains a major cause of childhood morbidity and mortality. WHO estimates that 1·2 million children (younger than 10 years) and young adolescents (aged between 10 years and 14 years) developed tuberculosis disease in 2022, although only half were reported to public health programmes.[1] Challenges in tuberculosis diagnosis are the major contributor to this case detection gap. Children have non-specific signs and symptoms of tuberculosis, and current pathogen-based testing has poor sensitivity in children because they frequently have paucibacillary disease (ie, with a relatively low bacterial load).[2] Host-based tests have variable performance in children as their immune response differs from that of adults.[3] Globally, 96% of tuberculosis deaths in individuals younger than 15 years occur in individuals not initiated on treatment.[4] Therefore, novel tests, intended for diagnosis or screening of tuberculosis infection or disease, are urgently needed to improve treatment access, reduce delays in care, and avert mortality. The WHO target product profile (TPP) for tuberculosis diagnostics outlines key test features to consider in children, including the ease of sample collection, use of non-sputum sample types, and applicability to pulmonary and extrapulmonary tuberculosis.[5]

Although the need is clear, new tests are typically not designed for the use in either children or adolescents. Furthermore, there are often delays in assessing and approving novel tuberculosis diagnostics for these groups. Even with increasing advocacy and guidance for childhood tuberculosis research, adult testing has been prioritised due to clearer reference standards, easier collection of samples, lower costs of enrolment, and ethical considerations of doing research in children. Moreover, adolescents frequently have adult-type disease but are often not included in adult studies. Because test performance data from children and adolescents are often late or insufficient, recommendations are commonly based on extrapolation of adult data. In summary, these issues lead to diagnostics being unavailable for these age groups or requiring providers to use tests outside their defined application and without guidance on their utility for tuberculosis diagnosis.[6]

Multiple stakeholders are involved in tuberculosis diagnostic design and evaluation, and there might be variable perspectives on the benefits, risks, and feasibility

Key messages

- A multistakeholder Delphi consensus process was completed to guide when and how children and adolescents should be included in the development and evaluation of new tuberculosis diagnostics
- 20 statements achieved consensus by stakeholders from academia, industry, non-profit organisations, government, funders, and advocacy groups
- The unique perspectives and needs of children and adolescents should be considered throughout the design and evaluation process of new tuberculosis diagnostics
- TB diagnostics should be evaluated in adolescents in parallel to adults
- Parallel evaluation in children should occur as early as possible, considering the type of test, potential benefits, and risks

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See Online for appendix

of including children and adolescents in these processes. Consensus is thus needed to guide best practices on when and how to include children and adolescents in the development and evaluation of novel tuberculosis diagnostics. A similar approach to therapeutic tuberculosis trials in children and pregnant individuals successfully facilitated earlier inclusion of these groups in these studies.[7,8]

Methods

We used a modified Delphi process with an international multidisciplinary group of stakeholders to reach consensus regarding the inclusion of children and adolescents in diagnostic development and evaluation studies for both pulmonary and extrapulmonary tuberculosis.[9] Diagnostic development was defined as the steps needed to create a diagnostic tool including the needs assessment, concept design, prototype development, feasibility assessment, and optimisation. Evaluation studies were defined as laboratory and clinical validation of a diagnostic tool once the design has been locked, and were divided into early and late stages.

The Delphi process was developed by a working group with expertise in childhood tuberculosis and experience in developing consensus statements (appendix p 2). Regarding participants in the consensus process, we aimed to have representation from academia (adult-focused and child-focused researchers), industry, non-profit organisations, government, advocates, regulators, and multilateral organisations, with prioritisation of individuals from or working in tuberculosis-endemic settings (appendix p 1). 57 individuals were invited from these categories based on expertise and background, with 23 (40%) of the 57 from or working in tuberculosis-endemic settings. Welphi software (Decision Eyes, Lisbon) was used to ensure that all responses were anonymous and to facilitate the iterative process.[10] Before starting, a bioethicist presented to participants an overview of the public health ethical framework, risk–harm–benefit evaluation, and the role of engagement with children and their caregivers in paediatric research.[11–13] The goal of the presentation was to provide a general framework for all participants who might have variable experience in considering ethical questions. The presentation did not comment on any specific topic or question from the consensus process.

The first qualitative round consisted of open questions informed by a review of the literature. The questions related to priorities for child and adolescent tuberculosis diagnostics and considerations during each stage of diagnostic development and evaluation (appendix pp 3–4). Children were defined as individuals aged 0–9 years, and adolescents were defined as individuals aged 10–19 years as per WHO guidance.[14] US National Institute of Health consensus definitions for childhood tuberculosis were referenced, including confirmed tuberculosis (microbiological confirmation by culture or WHO-approved molecular test), unconfirmed tuberculosis (no microbiological confirmation, but consideration of signs and symptoms of tuberculosis and response to treatment), and unlikely tuberculosis (other criteria not met).[15]

The working group did not participate in the consensus, but reviewed the responses, identified key themes, and generated draft statements. Each working group member independently reviewed the qualitative round responses and recorded key themes. Recurrent themes were then presented to the entire working group, who then discussed and drafted statements based on these themes. Statements were not made on themes that have been commented on in other documents, such as the WHO TPP for tuberculosis diagnostics.[5]

In the second and third rounds, participants were asked to vote on the statements using a Likert scale (1: disagree; 2: mostly disagree; 3: don't agree or disagree; 4: mostly agree; and 5: agree) or abstain, with comments requested if the participant disagreed or mostly disagreed. Consensus for a given statement was defined a priori as at least 75% of the participants scoring 4 or 5. Statements that did not achieve consensus were reviewed by the working group and revised according to the comments provided. Updated statements were presented to participants together with their previous responses and corresponding anonymous comments. Each round remained open until at least 85% of participants responded, with reminders sent via email. An open virtual dissemination meeting was organised in May, 2023, to share the results and receive feedback on considerations for implementation from a wider audience.

Results

42 (74%) of 57 invited participants contributed to the consensus process. The majority who agreed to participate worked in academia, but stakeholders from non-profit organisations, industry, government, funders, and advocacy were also included (appendix p 1). 15 participants (36%) were from tuberculosis-endemic settings. The response rates for rounds one, two, and three were 88%, 88%, and 90%, respectively. The final statements and the proportion of participants agreeing are shown in panel 1 and the appendix (pp 5–7) shows the distribution of responses in all rounds.

Diagnostic development

Participants agreed that feedback from children, adolescents, and their caregivers was key throughout the development and evaluation process (statement 1). As one participant explained: "Early-stage evaluations should make at least some assessment of the acceptability and usability of a diagnostic for children and adolescents so that design modifications can be made early, and the product can stay on the key path to commercialisation. In case this process is not done until late stage, the investment might be wasted, and developers might need to go back and repeat development steps."

Panel 1: **Consensus statements for inclusion of children and adolescents in tuberculosis diagnostic development and evaluation**

Diagnostic development

(1) Feedback from children, adolescents, and caregivers should be incorporated throughout the diagnostic, development, and evaluation process (95% agreement)
(2) Paediatric tuberculosis researchers should collaborate with developers in the design process to facilitate early connections to participants, data, and samples (97% agreement)
(3) The development of new tests with non-sputum samples for pulmonary and extrapulmonary tuberculosis should be prioritised (97% agreement)
(4) Tests designed for sputum should be evaluated in parallel for their utility in non-sputum sample types, when appropriate (91% agreement)
(5) Minimum specimen volume requirements should be considered and determined as part of the test design (97% agreement)
(6) For assay optimisation of new pathogen-based tests, adolescent and adult samples should be prioritised (84% agreement)
(7) Digital health innovations should be developed specifically for children, in parallel to those for adolescents or adults (87% agreement)
(8) At a minimum, early accuracy studies should compare symptomatic microbiologically confirmed child cases of tuberculosis to symptomatic children without tuberculosis (91% agreement)

Diagnostic evaluation

(9) Adolescents aged 10–19 years should be included in adult tuberculosis diagnostic studies (79% agreement)
(10) Accuracy data for tuberculosis diagnostics in adolescents should be presented separately from data from children and adults (84% agreement)
(11) Consensus reference standards should be used to define tuberculosis status in children for diagnostic development and evaluation (86% agreement)
(12) In early and late evaluation studies, diagnostic accuracy should be assessed against both a microbiological reference standard and a composite reference standard (92% agreement)

Early evaluation

(13) Pathogen-based tests should be evaluated in adolescents and adults first when performing the test or collecting the sample is greater than minimal risk in children (87% agreement)
(14) Pathogen-based tests should be evaluated in children in parallel to adolescents and adults when performing the test and collecting the sample is minimal risk (84% agreement)
(15) In case pathogen-based tests are evaluated in adults and adolescents first, evaluation in children should be initiated as soon as the test shows promise in adults (92% agreement)
(16) Tests based on host biomarkers should be evaluated in children in parallel to adults (84% agreement)
(17) Early evaluation of the accuracy of tuberculosis diagnostics in children should preferentially be done on well characterised banked samples, when available and suitable for the test (82% agreement)

Late evaluation

(18) Late evaluation of diagnostics for children should include prospectively collected samples (100% agreement)
(19) Diagnostic accuracy studies in children should aim to store well characterised samples in a well curated biorepository (89% agreement)
(20) In late evaluation and demonstration studies, the added yield of new tuberculosis diagnostics for children should be assessed in combination with other available testing and clinical algorithms (100% agreement)

Participants indicated that diagnostics for childhood and adolescent tuberculosis have unique implementation challenges and that the feasibility and acceptability of using these tests might differ from adults. The participants articulated that the involvement of social scientists and the use of systematic and iterative qualitative assessments (eg, interviews, surveys, and focus group discussions) would contribute to effective design and implementation of diagnostic tools for childhood and adolescent tuberculosis. The importance of a representative and diverse group of stakeholders and the value of involving community advisory boards to provide guidance and feedback in the design were also mentioned. The participants noted that it is not always easy to access these groups and that there is a need for developers and researchers in paediatric tuberculosis to collaborate early to ensure that new diagnostics are designed with input from children, adolescents, caregivers, and health-care providers who will use these tests (statement 2).

Participants were asked about unique characteristics to consider in the design of a tuberculosis diagnostic tool for children and adolescents (panel 2). The most common themes were related to the use of non-sputum samples and the consideration of minimum volume requirements during the design stage (statements 3–5). Participants agreed that assays developed for sputum should be assessed in non-sputum sample types if feasible. The importance of designing tests with the specific intention of analysing non-sputum sample types was also

Panel 2: **Summary of characteristics to consider in a tuberculosis diagnostic developed for children and adolescents**

Assay characteristics

- Prioritise sensitivity and positive predictive value
- When pathogen-based, able to detect low levels of *Mycobacterium tuberculosis*
- Adequate performance in key paediatric risk groups: malnutrition, HIV-positive, HIV-exposed but uninfected, and children younger than 5 years
- Ability to test different specimen types including respiratory and non-respiratory specimens

Specimen type and collection characteristics

- Easy to obtain, with minimal discomfort and pain, and no requirement for hospitalisation or fasting
- Option of self-collection or caregiver-collection
- Able to maintain privacy and confidentiality in collection, particularly for adolescents
- Preference for non-sputum and non-invasive sample types
- Minimal volume needs particularly for young children

emphasised (statement 3). As one participant stated: "The problem is that most diagnostics are developed for detecting tuberculosis in sputum, and then some data is generated on the use of these diagnostics in other samples, generally with lower accuracy. Starting with alternative sample types, however, will require innovation in boosting performance and perhaps greater exploration of new diagnostic methods/technologies appropriate for use among children, in terms of both accuracy and sampling/feasibility."

Many participants mentioned the importance of considering the ease of collection of a sample type and limiting the complexity of sample processing. Minimum volume requirements should be determined as early as possible to assess feasibility and risks for collection in children. Other general aspects mentioned by participants were the need for the test to have low cost, easy maintenance, and rapid results at the point of care, preferably at a primary care or lower-level facility.

For the early development of pathogen-based tests, defined as assays that detect *Mycobacterium tuberculosis*, its DNA, or other bacterial components, participants noted the advantages of adolescent and adult samples compared with child samples: clearer reference standard, higher number of microbiologically confirmed cases, and possibly improved availability of samples to support iterative testing (statement 6). The goal would be to optimise the detection of *M tuberculosis* antigens or DNA, with host characteristics not expected to influence this process. At the same time, participants noted that there should be a planned stratified analysis by level of bacterial load (such as molecular semi-quantitative result) to assess and optimise the test's performance in paucibacillary tuberculosis disease. Similarly, separate limit of detection studies should be done to assess the sensitivity of the assay to detect low-level *M tuberculosis*.

Children have a wide range of tuberculosis phenotypes that differ from those seen in adults, resulting in different clinical and radiological manifestations of the disease. Thus, participants reached consensus that digital health tools for tuberculosis, defined as tests that use digitised or electronic collection methods (such as images, sounds, or sensor monitoring data), should be developed specifically for children (statement 7). This implementation of digital health tools should be done in parallel to work in adolescents and adults, in whom disease manifestations are broadly similar. Non-invasive collection tools, such as sensors, recorders, or clinical and radiographical data collected as part of routine tuberculosis evaluation were noted to cause minimal additional harm to children and support their earlier inclusion in tuberculosis diagnostic development.

Developers of new tuberculosis tests might complete an early assessment of their accuracy as part of optimisation. At this stage, clear reference standards are essential, and there was consensus that (at a minimum) children with microbiologically confirmed tuberculosis should be evaluated to assess sensitivity (statement 8), while symptomatic children with unlikely tuberculosis should be used to assess specificity (to avoid overestimation of performance by using healthy controls).[15] The participants recognised the importance of clinically diagnosed, unconfirmed tuberculosis, as this group represents most paediatric tuberculosis cases. However, as this group is highly heterogeneous and might include children without true tuberculosis disease, we did not achieve consensus that the inclusion of children with unconfirmed tuberculosis was optimal in early accuracy assessment (74% agreement). Consensus was reached that children with unconfirmed tuberculosis should be included in early and late evaluation studies.

Diagnostic evaluation

Compared with children, adolescents are more likely to have a tuberculosis phenotype similar to adults, and participants reached consensus to include them in adult studies (statement 9). As one participant noted: "They can expectorate [sputum] and have a clinical presentation akin to adult [tuberculosis] and unlikely to be primary infections. Adult studies are more numerous and easier to conduct, which would facilitate evaluating the tests in larger groups of [older] children."

At the same time, participants commented that adolescents aged 10–19 years are not a homogeneous group, with unique issues varying across the age range with differences in acceptability of testing and sample types. To obtain useful results when adolescents are included in adult studies, participants stated that an inclusion target should be defined, stratified analyses should be done (statement 10), and acceptability

and feasibility should be assessed separately. Some participants mentioned that younger adolescents (ie, aged 10–13 years) might not be able to expectorate sputum and might be developmentally closer to children. The statement thus does not preclude the inclusion of adolescents in paediatric or adolescent-only studies, but rather highlights the benefits of including adolescents in adult studies to facilitate larger and faster evaluation.

Consistent with past guidance, participants agreed that international consensus reference definitions should be used to address the absence of a gold standard test in paediatric tuberculosis (statement 11).[15] The current approach is to classify children and adolescents as having confirmed tuberculosis, unconfirmed tuberculosis, or unlikely tuberculosis based on clinical, microbiological, and radiographical criteria at baseline and follow-up.[15] Participants noted the importance of including children with unconfirmed tuberculosis, while highlighting that this group represents a grey zone of classification. To address this need, consensus was reached in determining accuracy based on both a microbiological reference standard (unconfirmed tuberculosis defined as not tuberculosis) and a composite reference standard (unconfirmed tuberculosis defined as tuberculosis; statement 12). This approach would recognise the potential biases in both reference standards and provide an accuracy range.

Although important efforts have led to the establishment of consensus clinical case definitions, participants noted that some level of subjectivity remains in the classification, and meta-analysis can be complex because of the differences in interpretation between studies. Moreover, these case definitions only capture intrathoracic tuberculosis and defining extrapulmonary tuberculosis remains challenging.

Early evaluation

Early evaluation involves studies assessing the accuracy of a new test against the reference standard. Similar to assay optimisation, participants highlighted the challenges of early evaluation of pathogen-based tests in children versus adults and adolescents, including the small number of children with microbiologically confirmed tuberculosis and high costs of enrolling children and classifying their tuberculosis status. However, participants also noted the importance of including children in early evaluation as the interpretation of benefits of a given test might be different in children than in adults. As one participant noted: "A test that is no better than existing tests for adults may be incrementally or even significantly better for children." Additionally, including children could provide data on alternative sample types. One participant explained why the diagnostic pipeline should not start with adults first: "Developing tools specifically for children is critical if we are to innovate regarding the performance and appropriateness of tests. If we only adapt diagnostics from adults, we'll likely continue in the cycle of having tests with insufficient accuracy among children with paucibacillary disease."

Consensus was ultimately achieved by considering the risk of the test in children (statements 13 and 14). Minimal risk was defined per the US Food and Drug Administration in case "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[16] In case the sample collection and testing are of minimal risk, then early evaluation of new diagnostics should occur in parallel for children as adults and adolescents. When the risk is greater than minimal, there should be initial testing in adults and adolescents, and in case results are promising, evaluation should be quickly initiated in children (statement 15).

In contrast to pathogen-based testing, the performance of host-based tests in adults or adolescents might not be translatable to children given their unique immune response to *M tuberculosis*. Thus, consensus was reached that biomarker testing related to the host response to tuberculosis should be evaluated early in children in parallel to adults and adolescents (statement 16).

The use of banked samples from children previously enrolled in tuberculosis diagnostic studies has several advantages—no additional sample collection is required and the banked samples have already been classified to provide the needed sample size of children with and without tuberculosis. Thus, participants agreed that early evaluation should preferentially be done on well characterised banked samples, to reduce barriers to including children in an early assessment. (statement 17). However, participants noted that the samples must be of good quality and stored appropriately, with relevant clinical information and adequate disease phenotyping and classification. Even though several biobanks have been established, the representation of paediatric samples was noted to remain small. Moreover, not all tests can be done on banked specimens (eg, fingerprick blood or breath samples), in which case prospective sample collection and testing might be necessary.

Late evaluation

Late-stage evaluation involves the assessment of clinical performance of tests in settings and populations where the test will be used in practice. Although banked samples are useful for early accuracy studies, participants agreed that prospective evaluation is needed in late-stage evaluation studies (statement 18). Besides the potential benefit of using a fresh specimen, this approach would allow assessment in the settings and population where the test would be implemented. These data might also be needed for regulatory approval and national and international guideline endorsements. At the same time, consensus was reached that these studies should store

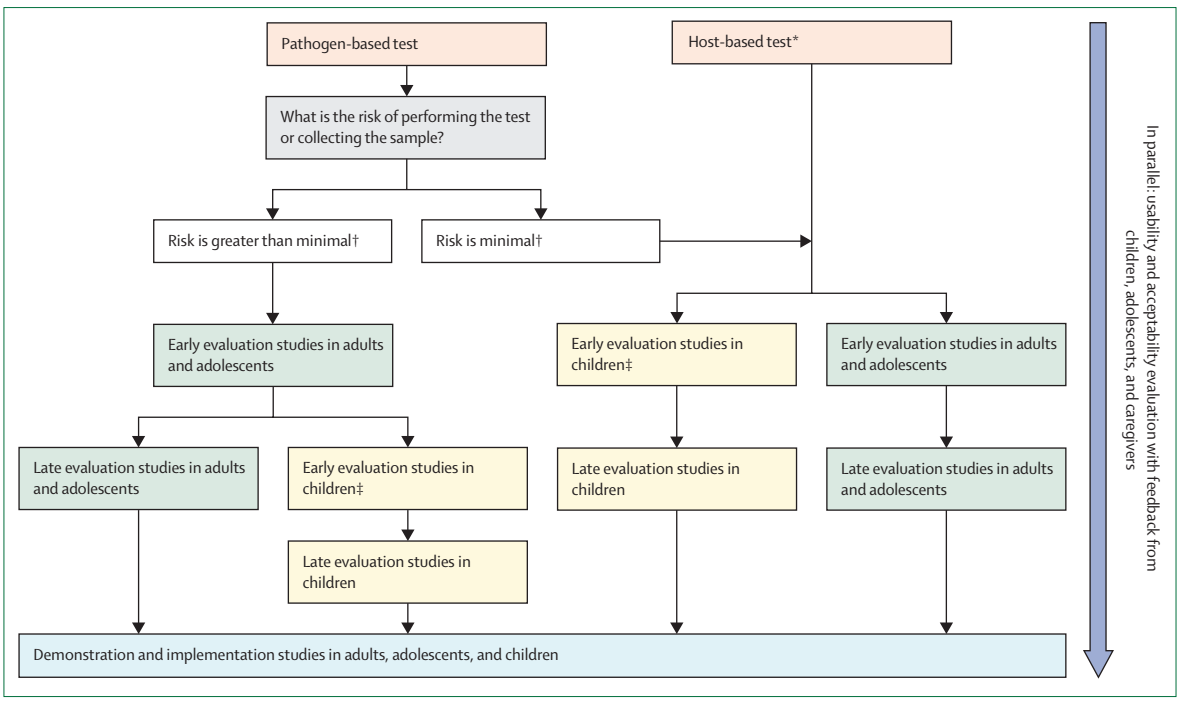

Figure: **Flow diagram to guide when children and adolescents should be included in the evaluation of novel tuberculosis diagnostics**
*Adult and adolescent data from host-based tests in adults are less likely to inform utility in children, and so risk has not been indicated to guide timing and prioritisation. However, the use of any test should consider the risk-to-benefit ratio. †Minimal risk defined as per US Food and Drug Administration (FDA).[16] ‡For early evaluation studies, biobanked specimens are preferred when appropriate.

additional or residual samples to support future diagnostic evaluation (statement 19).

Demonstration or implementation studies aim to assess whether evidence from controlled settings can be replicated during scale-up in terms of medical and public health benefits in the environment where the test will be used. For late evaluation, demonstration, and implementation studies, participants noted the importance of assessing diagnostics beyond accuracy. For example, a new diagnostic tool might not meet the optimal WHO TPP accuracy, but it might have value in case it increases the yield of tuberculosis diagnosis in children and adolescents. Moreover, novel tests should be assessed in comparison with and in combination with current tests and algorithms (statement 20). This evaluation includes measuring incremental yield after integrating the new diagnostic into treatment decision algorithms for children.[14] Consequently, providers and public health programmes can determine how a new diagnostic tool could be best utilised in the context of current evaluation guidelines. As one participant noted: "It is very important to make use of available tools in combination, and to develop the clinical pathways and algorithms most appropriate to take advantage of these tools [...] Combinations of tools should be evaluated taking into account 1) the optimal set of tools for triage and diagnosis, 2) the most appropriate test samples based on accuracy and ease/feasibility of sampling, and 3) the efficiency of the algorithm/diagnostic pathway taking into account time/financial burden on children and adolescents and their caregivers to reduce loss to follow-up [...]"

Dissemination meeting and summary flowchart

The figure summarises the approach to the evaluation of new diagnostic tests for children and adolescents based on the statements. There are four key aspects. First, adolescents are included in adult studies. Second, as early evaluation data from pathogen-based tests in adults and adolescents might inform utility in children, studies could be prioritised in adults and adolescents in case the sample collection or testing has greater than minimal risk. However, early evaluation should then proceed in children rapidly when the test performance is promising. Third, early and late evaluation of new diagnostics should occur in parallel for children, adolescents, and adults in case the test is: pathogen-based and minimal risk; or host-based, including immune biomarker assays and digital tools. Data from host-based tests in adults are less likely to inform use in children, so risk level has not been indicated to guide parallel versus sequential assessment, although the use of any test should consider the balance of risk and benefit. Lastly, this conceptual framework assumes that diagnostic evaluation is an iterative process and usability and acceptability feedback should be incorporated from children, adolescents, and their caregivers. With this approach, there should be sufficient data to support implementation studies in all age groups. Panel 3

provides an example of how this process could occur for molecular swab-based testing.

Discussion

Using an online Delphi process, stakeholders from academia, industry, government, funding agencies, and advocacy achieved consensus on an approach to include children and adolescents in tuberculosis diagnostic tool development and evaluation. The goal of the framework is not to restrict innovation for tuberculosis, but rather to advocate for earlier discussion on the potential indication for use in children and adolescents.

The consensus highlights that when developing a new diagnostic tool, discussion about its use in children and adolescents should ideally occur from conception. There should be an early partnership with experts in paediatric tuberculosis to discuss key priorities, including sample types and volume needs when applicable, and iterative feedback from children, adolescents, and their caregivers should be provided throughout the design process. This collaboration between developers, researchers, regulators, and users will also facilitate planning of early and late evaluation studies, including identifying banked samples and preparing for prospective assessment. Information on a test that does not meet the need or early performance targets for children and adolescents is also valuable, as it clarifies the scope of the test and reduces future harms and costs.

Our consensus process benefited from a range of stakeholders and statements were informed directly from the qualitative round. All rounds were anonymous and each vote had equivalent weight. We also had a public dissemination meeting to receive responses and feedback from a wider group of stakeholders, including additional individuals outside of academia and from tuberculosis-endemic settings. However, acknowledging the limitations of our consensus statement is important. We did not focus on implementation studies, but reducing delays in the assessment and approval of tests for children and adolescents would hopefully inform their earlier inclusion. We did not address specific diagnostics, as we sought a general approach that could be applied to current and future tests. Although the response rate was high, the number of participants was relatively small and might not be representative of all stakeholders. We would have benefited from greater representation of real-world implementors from tuberculosis-endemic countries and non-paediatric academic researchers; as a consequence there might be bias. A community advisory board did not participate in the process, but an important recommendation and future direction is to utilise the conceptual framework to further engage with a wider range of stakeholders including children, adolescents, their caregivers, health-care workers, representatives from non-governmental organisations and national tuberculosis programmes, and community advisory boards for ongoing discussion on the inclusion of children and adolescents in tuberculosis diagnostic tool development and evaluation.

New tuberculosis diagnostics for children and adolescents are clearly needed, but when and how to best include them in development and evaluation requires consideration of the risk and benefits and multi-stakeholder engagement and agreement. This consensus-based framework overall seeks to encourage early partnership to facilitate communication of the unique needs of children and adolescents, and to support planning of evaluation studies to reduce delays in access and improve care for children and adolescents with tuberculosis.

Panel 3: An example of how to apply the consensus framework to oral swab-based molecular testing

- Molecular tests for *Mycobacterium tuberculosis* detection from oral swabs are being developed. As part of the design process, developers collaborate with paediatric tuberculosis experts and receive feedback from children, adolescents, and caregivers regarding specimen collection protocols that are optimally acceptable and feasible.
- During assay optimisation for this pathogen-based test, developers prioritise the use of adult and adolescent samples, but perform stratified analysis by bacterial load and conduct separate limit of detection studies to assess potential utility in paucibacillary disease.
- After the design is locked and assay optimised to detect *M tuberculosis* in swabs, early evaluation studies begin. Since the risk of collecting oral swabs is minimal and its use would be of high interest for children as a non-invasive respiratory specimen, paediatric evaluation occurs in parallel to adults and adolescents. If feasible and suitable, well characterised banked swabs from children would facilitate faster and cheaper assessment.
- When the test is promising in children and adolescents, then late evaluation studies can proceed without delay. Guided by discussion with regulators and national and international guideline groups, this evaluation could include usability and acceptability data from children, adolescents, and caregivers, with assessment of test performance in combination with other tests and as part of relevant treatment decision algorithms.

Search strategy and selection criteria

To inform the questions for the qualitative round, we did a search of PubMed, Embase, and Google Scholar of articles published from January, 2011, to July, 2021, to identify guidelines, consensus statements, and best practices on the development and evaluation of tuberculosis diagnostics for children and adolescents. Search terms included "tuberculosis", "diagnosis", "development", "evaluation", "children", and "adolescents". We reviewed the relevant references and cited articles published in English.

Contributors

DJ, RS, and EMB conceptualised the project, with development of the process and analysis from the working group: EMB, LH, SL, ELM, BJM, MPN, LO, JAS, JSS, RS, HJZ, and DJ. Writing of the original draft was done by EMB, LH, SL, and DJ, with review and editing by all authors.

Declaration of interests

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