

## Tuberculosis 2019 2



# Challenges and controversies in childhood tuberculosis

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Children bear a substantial burden of suffering when it comes to tuberculosis. Ironically, they are often left out of the scientific and public health advances that have led to important improvements in tuberculosis diagnosis, treatment, and prevention over the past decade. This Series paper describes some of the challenges and controversies in paediatric tuberculosis, including the epidemiology and treatment of tuberculosis in children. Two areas in which substantial challenges and controversies exist (ie, diagnosis and prevention) are explored in more detail. This Series paper also offers possible solutions for including children in all efforts to end tuberculosis, with a focus on ensuring that the proper financial and human resources are in place to best serve children exposed to, infected with, and sick from all forms of tuberculosis.

### Introduction

An estimated 1 million children become sick with tuberculosis each year and most of these children are never diagnosed or treated for their disease.<sup>1</sup> With appropriate and timely treatment the prognosis for children with tuberculosis is excellent. However, because of gaps in diagnosis and linkage to care, mortality from tuberculosis in children is high.<sup>2</sup> As shown in the figure, modelling estimates suggest that as many as one in four children sick from tuberculosis will die from this disease.<sup>3</sup> Striking gaps in the diagnosis and treatment cascade are also apparent when considering rifampicin-resistant and multidrug-resistant forms of tuberculosis, in which fewer than 5% of the estimated 25 000–32 000 children who become sick each year<sup>4</sup> ever receive treatment.<sup>5</sup> Children are considered a vulnerable population and should be considered a priority in global approaches to improve diagnosis, treatment, and prevention of tuberculosis.<sup>6</sup> Since the 1970s, however, the public health approach focusing only on sputum smear-positive individuals led to children being excluded from larger tuberculosis control efforts.<sup>7</sup> This Series paper will explore some of the key challenges and controversies in approaches to paediatric tuberculosis and suggest some ways in which children can be prioritised in the era of WHO's EndTB strategy to end tuberculosis. An in-depth discussion of challenges and controversies in tuberculosis diagnosis in children is presented in panel 1 and in tuberculosis prevention in children in panel 2. Other relevant challenges in paediatric tuberculosis epidemiology and treatment are discussed briefly and summarised in panel 3; research priorities for paediatric tuberculosis are summarised in panel 4.

### Challenges and controversies in diagnosis of paediatric tuberculosis

For both drug-susceptible and drug-resistant forms of tuberculosis, screening for and diagnosis of disease in children is a challenge, especially in the younger age groups ( $\leq 5$  years).<sup>8</sup> Children might have extrapulmonary or paucibacillary tuberculosis and although many do

present with typical findings of pulmonary tuberculosis,<sup>9</sup> others are missed with diagnostic and screening strategies that were developed for adults.<sup>10</sup> Furthermore, many children with tuberculosis might be missed when they present for child-focused health services, including routine vaccinations and during screening for other health issues, including malnutrition and pneumonia.<sup>11</sup>

Although passive case finding for tuberculosis in children is clearly not sufficient, some controversies exist regarding how best to actively find children with tuberculosis disease. Some would advocate for a household-based approach wherein all children are screened whenever a household member is diagnosed with the disease.<sup>12</sup> Studies have shown, however, that most children with tuberculosis disease are not exposed in the household, leading some to advocate for a broader screening approach.<sup>13,14</sup> Others argue for targeted, non-household screening as in the malnutrition wards and the general paediatric hospital wards, especially among children diagnosed with pneumonia or malnutrition. Culture-confirmed tuberculosis has been shown in as

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This is the second in a [Series](#) of three papers about tuberculosis (paper 3 appears in *The Lancet Respiratory Medicine*)

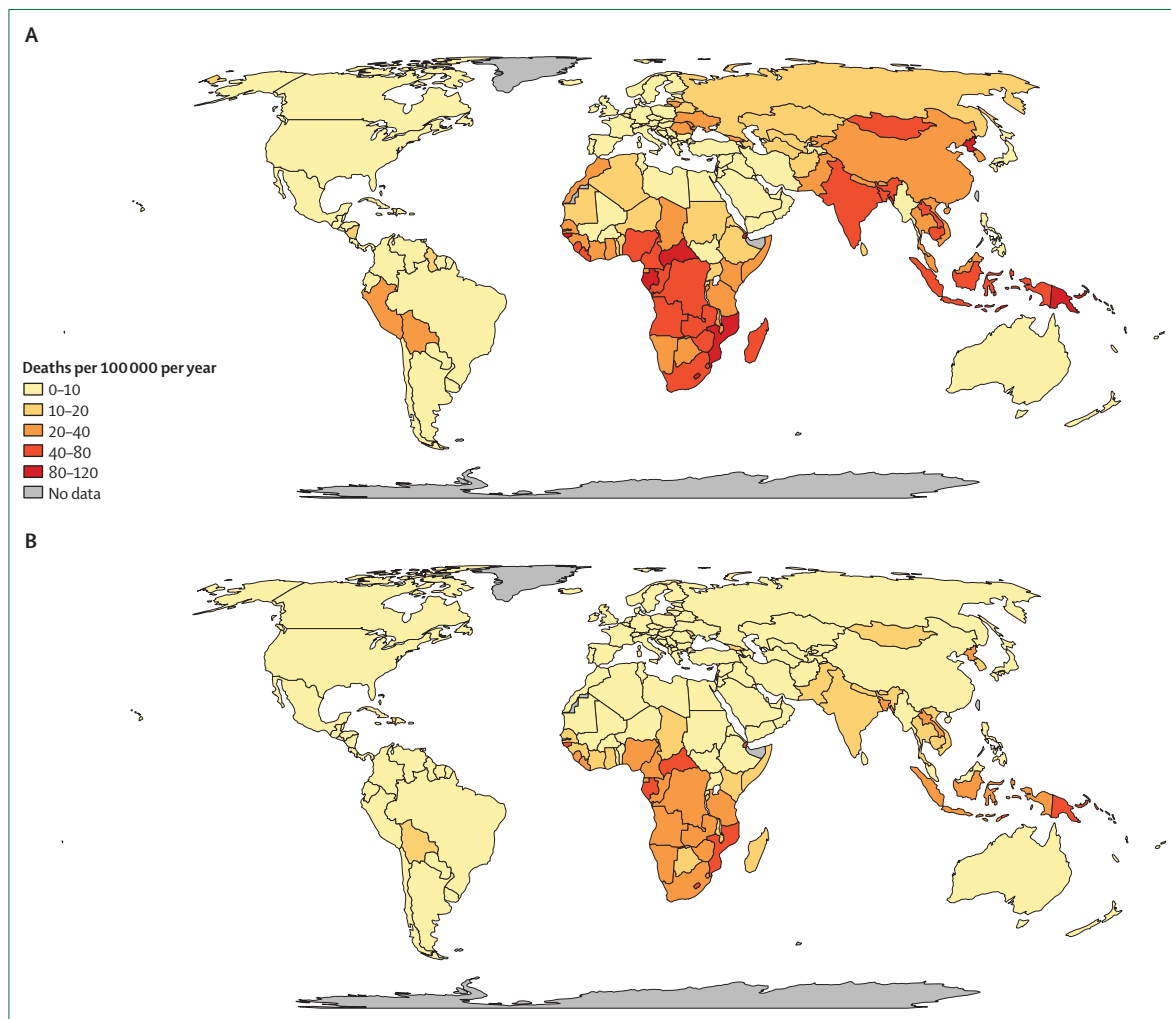
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### Search strategy and selection criteria

References for this Series paper were identified by searching the following databases: PubMed, OVID, and MEDLINE. Articles published in English, French, or Spanish between Jan 1, 2015, and April 1, 2019, were identified if they contained the following terms: "child/ren", "pediatric", "childhood", OR "adolescent" AND "tuberculosis", "drug-resistant", "diagnosis", "treatment", "prevention" and "clinical trials". With this strategy, more than 3000 articles were identified, and the abstracts of each of these were reviewed by one of the study authors (JF). Articles resulting from these searches and relevant references cited in those articles were selected if they included data from clinical trials, observational studies, or reviews. Those that contained case reports, focused on clinical presentation or manifestations, or suggested clinical management advice were generally not included. Some studies from before 2015 were included if they reported findings of key relevance to the diagnosis, treatment, or prevention of tuberculosis in children. Of note, the term rifampicin-resistant tuberculosis used in this Series paper is meant to encompass all forms of tuberculosis in which at least rifampicin resistance exists. The term multidrug-resistant tuberculosis includes rifampicin resistance but is specific to strains of tuberculosis that are also resistant to isoniazid.



**Figure:** Estimated global mortality from paediatric tuberculosis (reproduced from reference 3, by permission of Dodd and colleagues)  
 (A) Mortality among children under 5 years in 2015 (tuberculosis deaths in children per 100 000 children). (B) Mortality among children under 15 years in 2015 (tuberculosis deaths in children per 100 000 children).

many as 151 (1.58%) of 9450 children admitted with malnutrition in Zambia (a country with a tuberculosis incidence rate of 361 per 100 000 population in 2018), either as a dual diagnosis or as the underlying cause of the malnutrition.<sup>15</sup> Another targeted strategy would be to screen any child with failure to thrive or who has fallen off his or her growth curve for tuberculosis.<sup>16</sup>

Another controversy in the diagnosis of paediatric tuberculosis is identifying the optimal screening strategy to use, and this strategy might vary with different case finding approaches. Many would argue that symptom-based screening should be used to detect children in need of further diagnostic testing,<sup>17</sup> but a clear definition of the symptomatology used during screening is needed, including the duration that would be considered positive (ie, any cough *vs* cough for more than 2 weeks).<sup>18</sup> However, although chronic cough has been found to be the symptom most commonly associated with

tuberculosis in children,<sup>19</sup> many children later found to have tuberculosis had no reported symptoms.<sup>20</sup> A pragmatic screening algorithm for children who have been exposed to tuberculosis has been proposed by WHO and could be implemented widely as a potential solution to the challenge of how best to screen children for tuberculosis,<sup>21</sup> although this algorithm would need to be validated in broader screening approaches compared with the adult algorithm.

Another simple screening strategy would be to enquire if any adults are present in the household who have been recently diagnosed with tuberculosis. However, given the stigma and discrimination surrounding tuberculosis, families or caregivers might conceal this diagnosis.<sup>22</sup> To ask if any people in the house have been coughing might be better. Similar screening can be done during vaccination visits and other child health campaigns to increase child tuberculosis case finding.<sup>23</sup>

### Panel 1: Challenges and suggested ways forward in paediatric tuberculosis diagnosis

#### Household-based active case finding missing a majority of children with tuberculosis, but broader screening strategies resource intensive and might be low yield

- Use targeted screening (with the most optimal and feasible strategy depending on the context)—for example, in children admitted to hospital, malnourished children, children presenting for routine vaccination, and children who have fallen off their growth curves
- Ensure that tuberculosis clinics have the equipment to weigh and measure children as part of tuberculosis screening activities and routine tuberculosis care
- Joint case finding activities with child health programmes could bring increased funding and personnel at a primary care level
- Earlier identification of children could lead to better outcomes and decrease costs to patient, family, and the health system
- Partner with other child health initiatives to increase funding and deploy trained and paid lay health personnel

#### Symptom-based screening might miss some children with tuberculosis

- Use and adapt pragmatic screening algorithms that have done well in the field
- Ask if any adults in the household have tuberculosis or chronic cough because many children with tuberculosis live in households where adults have tuberculosis as well
- Consider imaging and physical examination to enhance the identification of children with extrapulmonary tuberculosis or atypical symptoms
- Consider imaging and physical examination for all children with documented tuberculosis exposure

#### Obtaining respiratory samples from children might be difficult

- Focus on induced sputum, gastric aspirate, and stool-based sampling methods

- Train and support health-care personnel, including at primary health-care level, to implement one method well, because obtaining one type of specimen over another does not appear to have clear benefits, although additional work is needed for stool-based methods

#### Additional data needed on other non-invasive samples, including urine, oral swabs, and serum

- National tuberculosis programmes should partner with academic and civil society groups to carry out pragmatic, operational research on these novel sampling methods to leverage expertise and resources

#### Multiple diagnostic tests exist with varying levels of data to support their use and to use them all will not be possible

- Prioritise the use of Xpert MTB/RIF Ultra and culture testing because these assays are the most sensitive and specific and also because they provide data on drug resistance
- National tuberculosis programmes should partner with academic and civil society groups to carry out pragmatic, operational research on novel diagnostic strategies to leverage expertise and resources

#### Bacteriological confirmation of tuberculosis disease in children is not always possible and empirical treatment of some children with tuberculosis is necessary, but risks for overtreatment and for undertreatment disease exist

- Monitor the proportion of children receiving tuberculosis treatment with bacteriological confirmation of tuberculosis and implement interventions to correct overtreatment and undertreatment

Some studies suggest that imaging could be used as both a screening and diagnostic tool for children who might have tuberculosis. Computer-assisted detection of tuberculosis with digital chest x-ray is becoming more important as a screening tool in adults.<sup>24</sup> This technology, however, has not been validated for use in children under 5 years. Point-of-care ultrasound has also been assessed as a possible screening and diagnostic tool for children with possible tuberculosis and has the advantage of being able to assess extrapulmonary forms of tuberculosis.<sup>25</sup> In addition to imaging, all children at risk of tuberculosis should undergo a basic physical examination including assessment of height and weight as part of tuberculosis screening. Unfortunately, many national tuberculosis programmes (NTPs) do not have sufficient human or financial resources to carry out such work and a need to identify and protect budget lines focused on children exists. Joining forces with those working in the child

health arena could facilitate resource mobilisation, and the use of paid and trained lay health personnel could increase the personnel involved in screening children for tuberculosis.

### Sample acquisition and testing

Although children can be diagnosed with possible or probable tuberculosis on the basis of history, symptoms, and physical examination,<sup>26</sup> NTPs and clinical providers also seek bacteriological confirmation of tuberculosis disease. This confirmation requires obtaining samples to test and deciding what types of tests will be done on these samples. Older children (>5 years) are more likely to have pulmonary disease than younger children and can usually produce a respiratory specimen, but for younger children (≤5 years) other respiratory specimens might need to be obtained (either through gastric aspirate or sputum induction) or non-respiratory specimens used, depending on the site of possible disease. When

**Panel 2: Challenges and suggested ways forward in paediatric tuberculosis prevention****Most vaccine trials focus on adults, and how these will work in younger children ( $\leq 5$  years) is unclear**

- Advocate for paediatric-specific vaccine trials and inclusion of older children ( $> 5$  years) and adolescents in adult trials

**Contact tracing often not done or involves only list making**

- Reinvalidate the idea of contact tracing as management after exposure and use this framework to advocate for national tuberculosis programmes to provide increased financial and human resources to identify, monitor, and manage children and adolescents who have been exposed to tuberculosis

**Not all children exposed to tuberculosis become infected and not all those who are infected become sick; however, no tests exist at the field level to identify children at high risk of developing tuberculosis disease**

- Use clinical exposure scales to supplement tests of infection to identify children who might benefit from preventive therapy
- National tuberculosis programmes can collaborate with research organisations to identify study priorities and maximise data collection in this area

**Broad implementation of treatment of infection (ie, preventive therapy or prophylaxis) is needed to decrease reservoir of people infected with tuberculosis, but challenges exist in implementing treatment of infection even in narrow populations**

- Adapt successful models of treatment of infection to local settings, including community-based services
- Ensure national tuberculosis programmes have the financial and human resources to carry out this expanded scope of work; strategies for doing this work could be to partner with those working in the field of universal health coverage and holding donors accountable for providing the resources to greatly expand tuberculosis prevention as agreed at the 2018 UN High-Level Meeting on tuberculosis

**Choice of regimen for the treatment of tuberculosis infection caused by rifampicin-susceptible tuberculosis now that multiple options exist but data are scarce on how they compare with one another or on their use in young children ( $\leq 5$  years)**

- Choose a regimen that is feasible in the local setting but that also takes into account the perspectives of the affected communities

**Treatment of infection for rifampicin-resistant and multidrug-resistant tuberculosis has been shown to be effective and cost-effective based on small observational studies but little certainty exists about which regimens to select**

- Implement screening after exposure to rapidly detect individuals with rifampicin-resistant and multidrug-resistant tuberculosis disease and also identify at-risk populations to be targeted for future implementation of treatment of rifampicin-resistant and multidrug-resistant tuberculosis infection once relevant trial results are available

**Results from randomised controlled trials to support widespread implementation of specific regimens for treatment of rifampicin-resistant and multidrug-resistant tuberculosis infection will probably not be available for another 5 years**

- Individuals at high risk should be considered for treatment of infection in the interim while waiting for more conclusive trial results
- Increased funding for national tuberculosis programmes, academic and implementing partners, civil society, and affected communities to carry out and assess this work could come from linking these activities to antimicrobial resistance work and funding

done correctly, both induction of sputum and gastric aspirate appear to have a sensitivity and specificity similar to spontaneously expectorated sputum in adults, and logistical attributes might determine which methods are best to use in programme settings.<sup>27</sup> Sending multiple samples for tuberculosis testing might increase diagnostic accuracy,<sup>28</sup> however, other studies found pooling of multiple samples did not increase diagnostic yield beyond that of a single high-quality gastric aspirate.<sup>29</sup> Increasing experience is being gained with stool specimens to diagnose tuberculosis in children,<sup>30,31</sup> and novel sampling strategies with a string test<sup>32</sup> or oral swabs<sup>33</sup> might gain prominence because additional data emerge on their use under programme conditions.

Once a specimen is obtained, several options exist for the types of tests that could be done on the specimen to assess for tuberculosis. Unfortunately, in many

contexts, most children's specimens are still assessed with only smear microscopy. This diagnostic test has low sensitivity and cannot provide any information on drug resistance.<sup>34</sup> Because as many as 70% of children with clinical tuberculosis disease are missed, smear microscopy should no longer be the test of choice for paediatric samples.<sup>35</sup> Rather the Xpert MTB/RIF assay (Cepheid, Sunnyvale CA, USA) with the Ultra cartridges or culture should be used for all children with possible tuberculosis.<sup>36,37</sup> Xpert MTB/RIF testing can be done on most samples (although its sensitivity and specificity are low in liquid from pleural effusions) and should be the test of choice for most paediatric samples and induced sputa.<sup>38</sup> This test has been shown to be useful under routine programme conditions,<sup>39</sup> although its role in testing urine samples from children has not yet been shown.<sup>40</sup> The urinary lipoarabinomannan test might also

### Panel 3: Challenges and suggested ways forward for other relevant issues in paediatric tuberculosis

#### Little information about the prevalence of tuberculosis in children

- Include adolescents (ages 10–19 years) in prevalence surveys of tuberculosis disease; report paediatric tuberculosis data disaggregated by age (ie, 0–5 years, 6–10 years, 11–14 years, and 15–19 years)

#### Fragmented approach to tuberculosis care in children given that those over 14 years are grouped with adults and those under 14 years are grouped all together as children

- Provide holistic and family-centred care tailored to the development needs of the different age groups

#### Little understanding of the optimal treatment regimens for children with all forms of tuberculosis

- Study and implement modified treatment regimens for children, with composition and duration on the basis of site and severity of disease
- Urgently assess dosing and safety of new drugs in children; fast-track access to new drugs that have been shown to be effective and safe in adults
- Increase public investment in research and development of paediatric-friendly drug formulations for tuberculosis and address country-level barriers to access and uptake of existing paediatric formulations

- Increase funding and capacity for national tuberculosis programmes to be able to treat children with the best available drugs and regimens

#### Children are often the last to benefit from tuberculosis science and innovation

- Increase funding and investment in paediatric-specific tuberculosis research and earlier inclusion of older children (>5 years) and adolescents in adult trials

#### Decentralised access to tuberculosis services for children is restricted

- Move away from routine hospital admission for treatment of all children with rifampicin-resistant and multidrug-resistant tuberculosis towards decentralised care; allow children to return to school and other activities in the community as quickly as possible
- Use paid community health workers
- Provide adequate funding and human resources for national tuberculosis programmes to implement decentralised care

be useful as a point-of-care, rule-in test for children (in a similar way as this test is used in patients admitted to hospital with low CD4 counts); however, additional data are needed to define its optimal use in paediatric tuberculosis.<sup>41</sup> The FujiFilm Silvamp Tuberculosis Lipoarabinomannan assay (FujiFilm, Tokyo, Japan) is also a promising urine-based test that could be used to support the diagnosis of tuberculosis in children because this test is more sensitive than other commercially available lipoarabinomannan tests.<sup>42</sup> Promising biomarkers also exist that could be used in tuberculosis diagnosis in the future, although most of these are far from being used in the field.<sup>43</sup>

One controversy in specimen acquisition and testing is how to optimise the multiple possible sampling strategies and diagnostic tools under programme conditions. Although to recommend obtaining multiple samples and doing multiple tests might be straightforward, NTPs do not usually have the resources available to them to undertake such work. A possible solution would be to focus on respiratory specimens (including those obtained from the gastrointestinal tract such as gastric aspirates and stool) and assess them with Xpert MTB/RIF Ultra cartridges and culture in paediatric patients, because these methods are the most sensitive and also provide information on drug resistance. Operational research assessing other samples and methods—such as on urine or oral swabs—could be done in collaboration with academic and civil society partners as well because these

### Panel 4: Research priorities for paediatric tuberculosis

#### Epidemiology

- Paediatric-focused prevalence surveys in selected settings with age-appropriate methods for clinical diagnosis and confirmation of tuberculosis disease

#### Diagnosis

- Assessment of tuberculosis screening algorithms that are independent of symptoms
- Development of sensitive and specific tests for bacteriological confirmation and resistance testing on stool, urine, and other specimens that are easy to obtain from children

#### Treatment

- Assessment of all oral regimens for children with all types of tuberculosis with duration of treatment on the basis of severity of disease
- Pharmacokinetic and safety studies of child-friendly formulations of tuberculosis medications

#### Prevention

- Inclusion of children in vaccine studies
- Development of sensitive and specific tests to determine tuberculosis infection and risk of progression to tuberculosis disease
- Assessment of treatment of infection regimens that are effective and safe in children of all ages

organisations could bring both human and financial resources to overburdened NTPs.

Another controversy in diagnostics is whether or not bacteriological confirmation is necessary for tuberculosis treatment in children. Although overdiagnosis of tuberculosis in children might be a problem in some settings (eg, children who have acute cough are started on antituberculosis therapy), in other settings tuberculosis is overlooked as the substantial cause of morbidity and mortality that it is.<sup>44</sup> As a consequence many children with tuberculosis are never diagnosed or never treated and many who die are not even counted as tuberculosis-related deaths.<sup>3</sup> Some studies have shown that empirical tuberculosis treatment in the absence of bacteriological confirmation is safe and effective.<sup>45</sup> This outcome might especially be true for rifampicin-resistant and multidrug-resistant tuberculosis, because providers might believe that children cannot become sick with these resistant forms of tuberculosis or are reluctant to start children on longer, more toxic rifampicin-resistant and multidrug-resistant tuberculosis treatment regimens than those used for drug-susceptible tuberculosis without proof that the child has drug-resistant tuberculosis.<sup>46</sup> Ironically, in some settings, young children ( $\leq 5$  years) whose parents or caregivers have been diagnosed with rifampicin-resistant and multidrug-resistant tuberculosis are started on treatment for drug-susceptible tuberculosis, with ensuing morbidity and mortality.<sup>47</sup> NTPs should carefully monitor the data on children who are started on tuberculosis treatment: if a high proportion of children have bacteriological confirmation then the programme is probably undertreating and needs to emphasise the importance of clinically diagnosed tuberculosis with front-line providers. Conversely, if a low proportion of children have bacteriological confirmation then the programme might need to focus on improving sample collection and testing in children.

### Vaccination and treatment of infection

Vaccination with BCG is an important way to prevent disseminated tuberculosis and tuberculosis meningitis, especially in children younger than 2 years; however, its wider role has yet to be realised.<sup>48</sup> Revaccination with BCG might be a way to improve its efficacy, and to overcome registration and cost barriers that might be associated with new vaccines, as seen in a randomised trial in HIV-negative children who had a negative QuantiFERON test (Qiagen, Hilden, Germany).<sup>49</sup> New vaccines are being developed, some of which have shown promise in preventing disease in adults and adolescents, who have become the focus of tuberculosis vaccination studies.<sup>50</sup> The exclusion of younger children ( $\leq 5$  years) from tuberculosis vaccine research is controversial and we do not fully understand how vaccines developed for older populations ( $> 5$  years) might or might not work in younger children.

An estimated 7.5 million children become newly infected with *Mycobacterium tuberculosis* every year, many

of whom will go on to develop tuberculosis disease. If these children are treated for tuberculosis infection (ie, given preventive therapy or prophylaxis), then their likelihood of developing tuberculosis disease is minimal. Children under 5 years and adolescents are particularly susceptible to developing tuberculosis disease but in many settings cannot routinely access interventions that could stop them from becoming sick.<sup>51</sup>

Children who have been exposed to tuberculosis are at high risk of developing tuberculosis disease. One way to find these children is through contact tracing and screening of household contacts when an adult has been newly diagnosed with tuberculosis, although data from 2019 suggest that non-household exposures are responsible for most childhood tuberculosis cases.<sup>52</sup> Furthermore, challenges exist in even defining what constitutes a household.<sup>53</sup> Contact tracing, however, rarely extends beyond list making, and little enthusiasm and few resources are dedicated to this crucial activity.<sup>54</sup> The low enthusiasm for contact tracing is often because of scarce resources within tuberculosis programmes; inadequate budgets and scarcity of staff who are expected to cover both tuberculosis treatment and prevention.<sup>55</sup> In most primary health-care settings, treatment of those ill with tuberculosis is prioritised over prevention efforts.

Reframing this essential tuberculosis prevention work as management after exposure could help to transform the approach to identifying, screening, and monitoring children who have been exposed to tuberculosis.<sup>56</sup> The change in terminology, however, would need to be more than cosmetic and NTPs must commit to bringing additional human and financial resources to the challenging work of systematically assessing all children and adolescents who have been exposed to tuberculosis and offering them treatment of infection. Modelling studies have estimated that such broad management after exposure to tuberculosis could prevent around 125 000 tuberculosis-related deaths and more than 300 000 new tuberculosis cases in adolescents and children.<sup>57</sup>

Whether or not to offer treatment of infection to all children with documented tuberculosis exposure is controversial in the field of tuberculosis. Treating all exposed children regardless of age or HIV status could reduce the tuberculosis reservoir but might not affect the natural course of disease in many individuals, could place children at risk of adverse events from the medications, and might use resources that would best be focused on high-risk individuals. Factors that favour restricting treatment to selected high-risk populations include the facts that some children who are exposed to tuberculosis do not become infected with the bacteria<sup>58</sup> and that data show that not all children who are infected go on to become sick with tuberculosis, although children aged 5 years and under and those living with HIV are at elevated risk.<sup>59</sup> Despite long-standing recommendations to offer treatment of infection for

children aged 5 years and under and those living with HIV, uptake has been minimal and multiple barriers exist to implementing treatment of infection even in this young population,<sup>60</sup> especially in settings in which the health-care system is stressed by other disease problems.<sup>61</sup> How could such flailing efforts be expanded to populations who are less likely to become sick and if they do, develop more mild forms of disease than children aged 5 years and younger?

Proponents for treating tuberculosis infection in all exposed children argue that no sensitive tests exist for tuberculosis infection,<sup>62,63</sup> and those that exist rely on a functional immune response, something that might be absent in children who are young, malnourished, or immunocompromised in other ways.<sup>64,65</sup> Tests of infection (including the tuberculin skin test, the C-Tb test, and interferon gamma releasing assays) are of less use in the paediatric population.<sup>66</sup> Data also exist showing that although the risk of tuberculosis disease and of severe forms of tuberculosis disease are higher in younger children ( $\leq 5$  years) than older children ( $> 5$  years), tuberculosis incidence rises again in adolescence.<sup>67</sup> Even though the risk of developing tuberculosis might be low in children aged 5–9 years, they still represent an important at-risk population in terms of absolute numbers.<sup>68</sup> Although some biological tests early in development exist that could be used to determine who will progress from infection to disease,<sup>69</sup> none of them are yet feasible for prospective use in programmatic settings in which children are assessed for tuberculosis. Nevertheless, successful implementation of treatment of tuberculosis infection has been done even in high-burden and high-risk settings,<sup>70</sup> including with the use of community health workers in decentralised settings,<sup>71</sup> and such programmes could be replicated elsewhere.

Although a need for tailored research to better identify risk factors and tests for tuberculosis infection and progression to disease clearly exist, clarity in these areas will probably take decades. In the meantime, advocacy for increased attention to and funding of efforts of management after exposure, including treatment of infection, is necessary for progress in tuberculosis elimination. Some of these efforts should be linked to universal health coverage and in this way expand the pool of available funding outside of those usually available for tuberculosis.<sup>72</sup> Community-based models of care could be replicated, and programmes could focus on operational field assessments to identify successful strategies<sup>73</sup> that can be replicated as programmes move in a stepwise fashion to widen the circle of those treated for tuberculosis infection.

Although selecting populations to be treated for tuberculosis infection is complicated, controversies also exist around which treatments to use. Multiple potential regimens, including 6–9 months of daily isoniazid, 4 months of daily rifampicin, and 3 months of daily isoniazid and rifampicin, can be given to children who

have been exposed to tuberculosis but not diagnosed as having tuberculosis disease.<sup>74</sup> Not all of these regimens have been compared with one another, and thus to know which regimen to select might be complicated. The lower medication costs of isoniazid compared with rifapentine and rifampicin, for example, could be outweighed by its higher rates of adverse events and lower rates of completion than rifapentine and rifampicin when used in extended regimens as a single agent. Additional research is needed to identify which regimens are most acceptable to patients and programmes, including qualitative and mixed-methods research. Concerns also exist about the possibility of reinfection with *M tuberculosis* in high-burden settings, and although a clear mortality benefit has been reported even with single courses of preventive therapy, additional work is needed to determine optimal prevention strategies where the prevalence of tuberculosis is high.<sup>75</sup> The ongoing WHIP3 tuberculosis study (NCT02980016) looking at cycled courses of treatment for tuberculosis infection in high-risk populations will hopefully provide additional information on the benefits of treatment of infection in the context of probable re-exposure.<sup>76</sup>

The short and highly effective rifapentine-based regimens that have been shown to be effective in adults, including the 12-week regimen of once weekly isoniazid and rifapentine and the 4-week regimen of daily isoniazid and rifapentine, are not routinely recommended for children.<sup>77</sup> The optimal dosing and safety of rifapentine has not been determined in children aged 2 years and younger, even though regimens containing rifapentine have been reported to be safe and effective in adults since 2011; a planned study on rifapentine dosing and safety in children aged 2 years and younger has been substantially delayed but will use a paediatric formulation of rifapentine. The benefits of these short regimens compared with the 3-month regimens of daily isoniazid and rifampicin or 4 months of daily rifampicin have not yet been established and would be important to study in children and adolescents, especially considering the implications of missing a weekly dose in the 12-week isoniazid and rifapentine regimen compared with missing a daily dose of the other regimens.

Another area of substantial controversy is the treatment of infection in people who have been exposed to rifampicin-resistant and multidrug-resistant tuberculosis. Some argue that although the risk of infection with rifampicin-resistant and multidrug-resistant tuberculosis might be high, the risk of progression to rifampicin-resistant and multidrug-resistant tuberculosis disease in children who are exposed has not been established<sup>78</sup> and to wait for the results of ongoing phase III trials would be better. Three ongoing clinical trials (V-QUIN [ACTRN12616000215426], TB-CHAMP [ISRCTN92634082], and PHOENIX [NCT03568383]) are investigating single-agent prophylaxis for people who have been exposed to rifampicin-resistant and multidrug-resistant tuberculosis in their households. Results from these

studies are anticipated in the next 5 years.<sup>79</sup> Because multidrug regimens are often used for the treatment of infection with rifampicin-resistant and multidrug-resistant tuberculosis, an increased risk of adverse events might exist that some experts feel mandates a test of infection before administration of such treatment.

Others counter that given the morbidity and mortality associated with rifampicin-resistant and multidrug-resistant tuberculosis, the risk–benefit ratio most certainly favours treatment of infection in paediatric populations exposed to this disease. The fluoroquinolones have an established safety record in children,<sup>80</sup> and given how poorly tests of infection do in the highest risk children, they should not be required before administration of such therapy. Multiple smaller observational studies and a meta-analysis have shown multidrug, fluoroquinolone-based regimens to be effective in preventing the development of tuberculosis among children and adults exposed to rifampicin-resistant and multidrug-resistant tuberculosis,<sup>81</sup> and in 2018 WHO recommended preventive therapy of rifampicin-monoresistant and multidrug-resistant tuberculosis for high-risk contacts of people exposed to rifampicin-resistant and multidrug-resistant tuberculosis in the household. Additional studies have also shown that implementation of such regimens is feasible, even in high-burden settings of rifampicin-resistant and multidrug-resistant tuberculosis.<sup>82,83</sup> Unfortunately, few countries and programmes offer this life-saving therapy and its use is limited only to pilot settings or wealthy countries.<sup>84</sup>

One potential solution to this controversy would be to emphasise the urgent assessment of all people exposed to rifampicin-resistant and multidrug-resistant tuberculosis to rule out clinical tuberculosis disease. This assessment would help to identify populations at highest risk of developing disease, potentially reducing the morbidity and mortality of rifampicin-resistant and multidrug-resistant tuberculosis through early identification of the disease. This approach would also begin laying a foundation for treatment of infection. Time is needed to establish such programmes. Additional information on optimal regimens for treatment of rifampicin-resistant and multidrug-resistant tuberculosis infection will probably emerge in that time and then could be rapidly deployed through these newly strengthened networks.<sup>85</sup> Very high-risk populations (ie, children aged 5 years and under and people living with HIV) could also be offered treatment of infection as these efforts advance. Linking these efforts to the global antimicrobial resistance strategy<sup>86</sup> could provide programmes with the human and financial resources that are clearly necessary to successfully address the substantial burden of rifampicin-resistant and multidrug-resistant tuberculosis infection.<sup>87</sup>

### Definitions, epidemiology, and treatment

One key challenge in paediatric tuberculosis is scarcity of robust prevalence data. The term paediatric itself can be

controversial, with various stakeholders defining the paediatric population as those under 18 years,<sup>88</sup> those under 15 years,<sup>89</sup> and those under 24 years.<sup>90</sup> Variable interpretation of the terms children, youth, and adolescents makes standardised reporting difficult. Because of the scarcity of definitive microbiological confirmation of tuberculosis disease, children under 14 years are often excluded from disease prevalence surveys,<sup>91</sup> and although many countries collect data on screening, diagnosis, and treatment of tuberculosis in children by age bands, they are not reported to WHO in this way. These issues continue to make reporting on the numbers of children who become sick with tuberculosis each year challenging. Although no routine data on tuberculosis prevalence have been reported, the figure shows the estimated global mortality from paediatric tuberculosis.

The one-size-fits-all model for tuberculosis treatment might not be ideal for children.<sup>92</sup> Those with isolated lymph node or simple pulmonary disease might require a short duration of treatment with few drugs,<sup>93</sup> whereas certain forms of severe tuberculosis disease (eg, tuberculosis meningitis) might require lengthy therapy with additional drugs that penetrate the central nervous system.<sup>94</sup> Some medications that are routinely given to adults might be too toxic to routinely administer to children, an example of which is the injectable agent class that had been recommended for the treatment of rifampicin-resistant and multidrug-resistant tuberculosis.<sup>95–97</sup> One controversial treatment challenge is that children are often denied access to new tuberculosis medications, usually because of dosing and safety concerns,<sup>98</sup> whereas medications that are no longer recommended in adults because of shown efficacy and safety concerns continue to be used in paediatric treatment.<sup>99</sup> A second challenge in paediatric tuberculosis treatment is the continued use of adult formulations of many of the first-line and second-line tuberculosis drugs for children.<sup>100</sup> Cutting, crushing, and mixing adult tablets to administer them to children results in inaccurate dosing and violates both Good Clinical Practice and Good Pharmacy Practice.<sup>101</sup> Progress has been made in the availability and use of paediatric-specific fixed dose combinations of the first-line tuberculosis drugs,<sup>102</sup> and uptake of paediatric second-line drug formulations through the Stop Tuberculosis Partnership's Global Drug Facility's Paediatric Drug-Resistant Tuberculosis Initiative is taking off in 17 countries. Major barriers to use of paediatric formulations are cost, because tablets used for adult treatment are often cheaper than child-friendly versions of the medications, and registration of paediatric formulations with regulatory authorities. A need exists to fund both paediatric-specific research studies and the inclusion of children and adolescents in adult tuberculosis treatment trials to avoid delays in access to innovation for this susceptible population.<sup>103–105</sup> Community consultation with children and their caregivers is essential to ensure that the studies minimise risk, answer questions of



importance to the target population, and take into account the affected communities' points of view.<sup>106</sup>

Children are often admitted to hospital for the treatment of tuberculosis because of undue fears about contagion.<sup>107</sup> Admission to hospital for treatment denies them access to school and to social and extracurricular activities, often perpetuating stigma and discrimination. Care in the community is more patient-centred and cost-effective for children and their families living with tuberculosis than hospital care, and decentralised treatment of all forms of tuberculosis has been associated with a faster time to treatment initiation and improved treatment outcomes than hospital treatment.<sup>108,109</sup> However, children with tuberculosis, especially those with rifampicin-resistant and multidrug-resistant tuberculosis, are often admitted to hospital for treatment away from their families and normal routines for months at a time. Obstacles to the decentralisation of paediatric care include a scarcity of access to paediatric tuberculosis expertise at the primary health-care level, little confidence in drug administration, poor access to child-friendly formulations of drugs, and the numerous social and economic problems faced by families whose children have tuberculosis.<sup>110</sup> In one study in which paediatric tuberculosis diagnosis and treatment was strengthened at a primary health-care level, tuberculosis case detection doubled, and paediatric tuberculosis treatment outcomes improved as did child contact screening and management.<sup>111</sup>

One important issue to address in all paediatric models of tuberculosis care is how to improve adherence support.<sup>112</sup> Adherence in children can be more complex than in adults and relies on a multidirectional relationship between the child, the child's primary caregivers, and the health-care providers. Age-appropriate counselling and support needs to be provided at each of these three levels, and individualised incentives and enablers should be offered to meet the unique needs of the age group.<sup>113</sup> Although toys or stickers might be appropriate for young children to encourage adherence, incentives such as telephone air time might be more appropriate for adolescents. Adherence support should also take into account the life goals and plans for children at all ages.<sup>114</sup> Excellent models of decentralised paediatric care have been developed in the field of HIV and could be adapted for use in paediatric tuberculosis.<sup>115</sup> Paid and trained community health workers are essential for successful decentralised care, case finding, case holding, and adherence support.<sup>116,117</sup>

## Conclusions

A reason for optimism exists in the field of childhood tuberculosis, because most children who are promptly diagnosed and started on effective therapy thrive when they are treated for their disease. In spite of this, the diagnosis and management of children with tuberculosis can be difficult, and challenges abound, especially in diagnosis and prevention of tuberculosis. However, one

thing is clear: if we as a global community are serious about ending tuberculosis and reducing tuberculosis-related suffering, care can no longer be aimed at predominantly adult populations. A comprehensive child and family-friendly approach is needed with improvements in tuberculosis screening strategies, diagnostic tools for children, models of care in which the needs of the child are placed ahead of the needs of the health system, adaptable treatment approaches for both tuberculosis infection and disease, and paediatric formulations of drugs with proven efficacy and reduced toxicity. Overt investment in paediatric tuberculosis research and development and access to the highest standard of care for all children, no matter their ages or where they live in the world, needs to become a global priority.<sup>118</sup> Finally, NTPs must be mobilised and committed to care for children and given the human and financial resources needed to implement the care necessary for this vulnerable group. Humanity has little hope for future tuberculosis elimination unless children are prioritised in every area. In the words of the late Nelson Mandela: "Our children are our greatest treasure. They are our future."

## Contributors

AR, JH, and JF contributed equally to the drafting and revision of the manuscript. JF primarily reviewed the literature with input from AR and JH.

## Declarations of interests

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