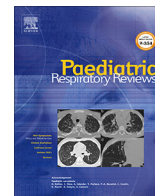




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Paediatric Respiratory Reviews



Mini-Symposium: Tuberculosis

Preventing tuberculosis in children: A global health emergency

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Educational aims

The reader will come to appreciate:

- The challenges and solutions associated with the TB prevention cascade.
- An approach to post exposure management and treatment options for drug-susceptible and RR/MDR-TB infection.
- The actions required from the paediatric community to reach “TB elimination” within ‘our’ lifetime.

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ABSTRACT

It is estimated that 20 million children are exposed to tuberculosis (TB) each year, making TB a global paediatric health emergency. TB preventative efforts have long been overlooked. With the view of achieving “TB elimination” in “our lifetime”, this paper explores challenges and potential solutions in the TB prevention cascade, including identifying children who have been exposed to TB; detecting TB infection in these children; identifying those at highest risk of progressing to disease; implementing treatment of TB infection; and mobilizing multiple stakeholders support to successfully prevent TB.

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INTRODUCTION

Children bear a substantial burden of the global tuberculosis (TB) burden, with more than one million (<15 years) becoming sick each year. While much attention has focused on the significant diagnostic challenges that characterize paediatric TB, most children needing evaluation for TB disease are not identified by health services, and 90% of the 205,000 children estimated to die from TB each year are never diagnosed or treated. TB prevention in this vulnerable population is also overlooked and constitutes a global health emergency [1]. Although the exact numbers of children exposed to TB each year is unknown, given the average household size and the number of incident adult cases, modeling suggests that as many as 20 million children are exposed to TB annually and 7.5 million child household contacts should be evaluated each year [2]. Yet most of these children receive no screening or TB

infection treatment. Global data show that fewer than 23% of children under the age of five years who were eligible for TB infection treatment (i.e. “preventive therapy”) received this basic intervention in 2017 [3].

With the global goal to eliminate TB within ‘our lifetime’, intensive and concerted actions need to prevent disease if there is any hope of “ending TB” [4–6]. Since children are a vulnerable population to TB that has been systematically overlooked in past TB control efforts, they should be prioritized when it comes to TB prevention [7]. In order for this to happen, multiple challenges must be addressed [8], including finding children who have been exposed to TB; detecting TB infection in these children (or using close exposure as a proxy for infection); identifying those at highest risk of progressing to disease; implementing treatment of TB infection; and galvanizing multiple stakeholders to support success. This paper will address each of these areas, with an eye toward rapid acceleration of paediatric TB preventive efforts (Fig. 1). Recommendations for action are summarized in Table 4 at the end of the paper. Because vaccines and enhanced diagnostics

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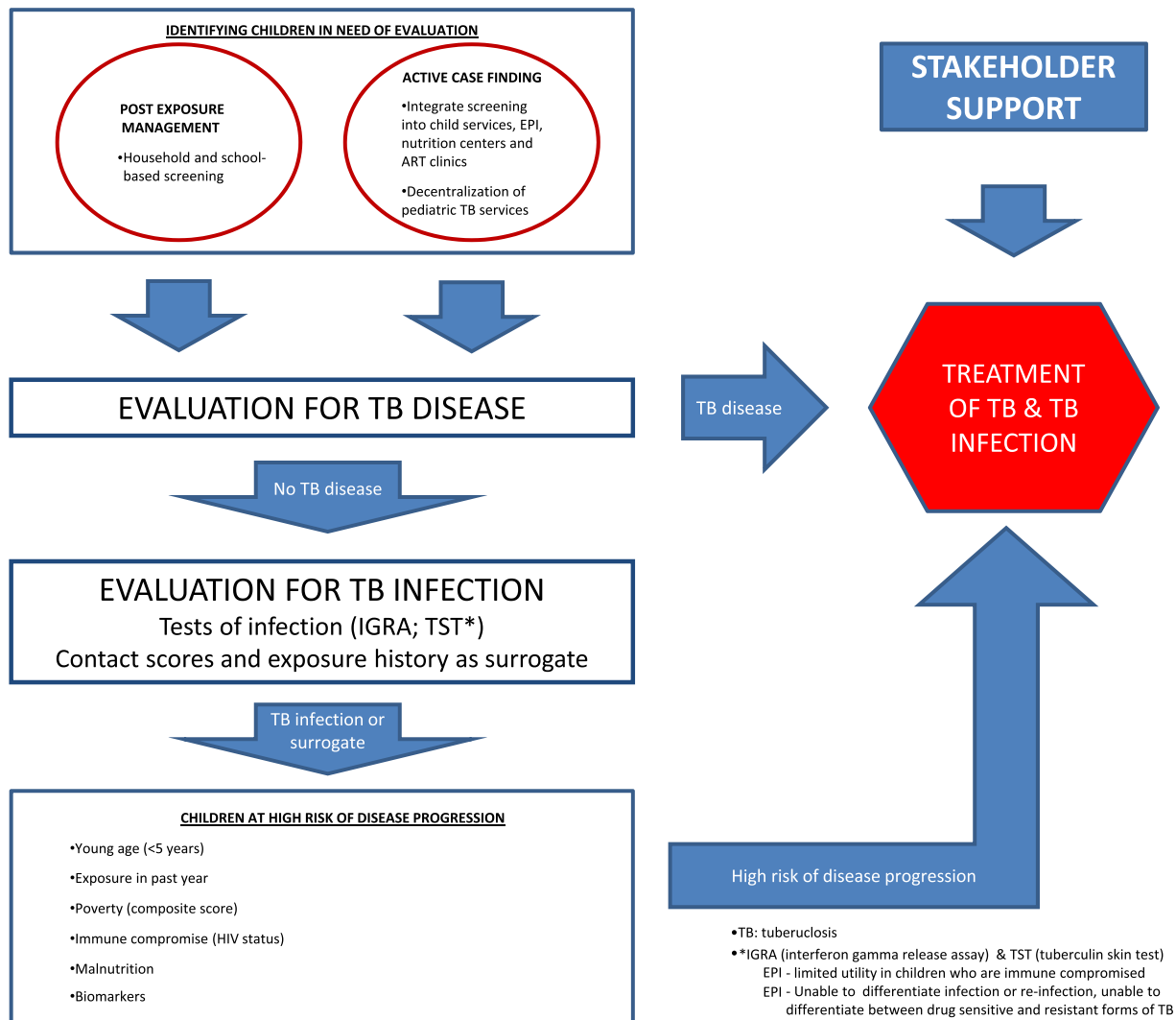


Fig. 1. Summary of main issues in TB prevention.

strategies are discussed in detail in other articles in this mini-symposium, they will not be addressed in this paper.

SEARCH STRATEGY AND TERMINOLOGY

We performed a review of the published literature on paediatric TB prevention using both PubMed and Ovid databases up to and including October 28, 2019. We also assessed relevant references from the papers identified and considered our combined clinical experience, working in many different settings. There are multiple definitions of “children” that are used in the TB and public health literature. In the field of TB, the World Health Organization (WHO) defines children as those who are under the age of 15 years, since they traditionally use 10-year age brackets and those aged 15 years and above tend to have adult-type disease [9]. However, given the transition in disease pathogenesis and unique adherence risk factors in the adolescent population [10], we defined children as individuals under the age of 18 years of age [11]. Other terms to clarify include “treatment of infection” instead of “preventive therapy” or “prophylaxis”. This term more clearly describes what is being done when a child is given medication in an attempt to eradicate the small numbers of *Mycobacterium tuberculosis* (MTB) organisms infecting his or her lungs prior to them causing TB disease [12]. It is acknowledged that vulnerable young children who

are household contacts of an infectious TB patient may receive ‘treatment of infection’, without proof of infection, using close exposure as a proxy of likely infection. Previous pathophysiologic descriptions differentiated “latent” and “active” TB, but more recent studies emphasize the spectrum of TB disease ranging from asymptomatic infection, to subclinical or incipient TB, to symptomatic TB disease [4]. We also prefer the term “post-exposure management” to that of “contact tracing” as it more accurately reflects the active nature of the work that is required after an individual has been exposed to an infectious TB case [13].

FINDING CHILDREN IN NEED OF TB PREVENTIVE SERVICES

One of the most important activities in paediatric TB prevention is the identification of children who may benefit from TB infection treatment [14]. It was traditionally thought that the majority of childhood TB is transmitted within the household [15,16], but emerging epidemiological evidence indicates a need to identify children infected with TB outside of their households as well. Despite this new insight, household contact assessment and treatment have been shown to be a highly effective in preventing vulnerable young children from getting TB and there is an urgent need for this to be up-scaled [17,18]. However, multiple barriers have been described to the implementation of TB prevention in

household settings, including the view that such work is a low priority activity for overburdened health systems [19]. Reframing contact tracing as “post exposure management” may increase both enthusiasm and funding for it [20], as seen in model projects from Pakistan and Peru [21,22].

A recent review looking at 13 studies – including a range of molecular and mathematical modeling, conversion studies and tuberculosis infection and progression to disease surveys—came to the conclusion that most transmission occurs outside of the household (population-attributable fraction of TB being 10–30% in households, as well as <30% in children under 5 [23]). This makes sense since the population of children exposed to TB within the household is relatively small compared with the global population of children. Thus, while household contact assessment is an important and high-yield activity to identify children in need of TB preventive services [24,25] and efforts in this area need to be stepped up, the data from these studies also beg the question of how can other children at risk of TB be identified?

Active case finding (ACF) is one important way to try and identify children in need of TB treatment, including treatment of infection [26]. Most ACF efforts, however, are only focused on finding children who are sick with TB disease [27]. While linking TB diagnosis and treatment with other child health interventions—including immunization and maternal/child health services—has been shown to be effective, [28,29] very few of these interventions focus on implementing TB prevention. School-based TB screening, including screening for TB infection, may be effective, but it is thought to be a relatively low-risk population and there is limited experience and evidence to guide interventions within the educational system [30]. Decentralization of paediatric TB services has been linked with an increased uptake of TB infection and disease treatment [31], but there are only limited interventions for TB infection treatment that occur outside of a post-exposure setting [32].

Ruling out active TB disease is essential [28] when identifying children who would benefit from TB prevention services [33]. Rapid identification of children who have TB disease and initiation of effective therapy are important means to prevent morbidity and mortality from the disease. Advances in the diagnosis of children with TB are discussed in another paper in this mini-symposium and thus they will not be addressed here.

DETECTING TB INFECTION

A crucial element of successful TB prevention is being able to identify children that are infected with *MTB*. Currently there are two types of commercially available tests of infection – the tuberculin (purified protein derivative or PPD) skin test (TST) and the serum interferon-gamma releasing assays (IGRAs) [34]. Unfortunately, both tests measure an immune response to TB and thus perform poorly in children who are immunocompromised and most vulnerable to TB, including those with HIV infection or malnutrition [35,36]. Because a negative test does not rule out TB infection – and because access to these tests is limited due to costs and availability in many high TB-burden settings – the *WHO Latent TB infection: updated and consolidated guidelines for programmatic management* specify that a test of infection is not a prerequisite to initiating treatment of infection in a high risk situations [37]. New tests of infection are being developed, but will require high sensitivity, low cost and simple point-of-care deployment to offer any advantage over what is already available [38,39].

In the absence of a sensitive and specific test of infection, close TB exposure may offer a reliable surrogate measure of TB infection. Contact scores that use routinely collected data such as (a) maternal TB; (b) sleep proximity; (c) smear status of the index case; and (d) duration and intensity of exposure can be used to predict TB infection and guide TB infection treatment [40]. Table 1 summarizes the advantages and disadvantages of the various methods for detecting TB infection in children.

IDENTIFYING CHILDREN AT HIGH RISK OF DISEASE PROGRESSION

All children with TB infection are in need of comprehensive TB services, but some groups of children are at higher risk of developing TB disease after they have been infected and require more urgent intervention. Factors associated with progression from TB infection to disease in children are summarized in Table 2 and include age (with those under 5 years of age being most at risk [41]), comorbidities that compromise the immune system such as HIV infection, malnutrition and other chronic illnesses, as well as socioeconomic deprivation in general [42]. One study found a composite score including measures of poverty (low household income, indoor

Table 1
Tools for assessing TB infection.

Tool	Benefits	Limitations	Future directions
<i>Tuberculin Skin Test</i>	Increased risk of TB disease in persons with positive test, allowing for targeted preventive therapy	Frequent global shortages; requires functioning immune system; potential for false positive tests with recent BCG vaccination; potential for false negatives in young children and individuals with HIV infection; requires in-person follow up for reading	Use of more specific TB-related proteins Likely to become less relevant in the future
<i>Interferon Gamma Releasing Assay</i>	No need to return for interpretation Quantifying changes over time could allow for targeted preventive therapy	High cost; requires functioning immune system; blood sampling can be difficult in small children; sensitivity not as well established in young children	Improve understanding of quantitative thresholds Use in smaller volumes of blood
<i>TB Exposure Scales</i>	Require no medical procedures; can be used by a variety of providers; Relatively easy to implement; accounts for risk factors related to source patient, environment, and exposed individual	Can be subjective and prone to recall bias; not yet shown to be strongly associated with TB infection or disease risk	Validate scales in prospective fashion
<i>Biomarker signatures</i>	Could be a more sensitive and specific marker for future TB disease progression	In early stages of development – promising results – no clear benefit demonstrated compared to IGRAs; none specifically developed for children; none associated with TB infection or disease in a prospective fashion	Continue validating work Identify potential signatures in children of all ages

TB: tuberculosis; BCG: Bacillus Calmette–Guérin; HIV: human immunodeficiency virus; IGRA: interferon-gamma releasing assays.

Table 2
Risk factors for progression to TB disease following documented exposure/infection.

Risk factor	Risk
Age	<5 years (especially <2 years) at high risk of disease progression as well as increased risk for development of disseminated and severe disease Adolescents at increased risk of disease progression as well as increased risk for development of adult-like disease
Immune status	HIV-positive, especially those not on ART and with severe immunosuppression; recent measles; immunosuppressant medications
Time since exposure	Most disease occurs within 12 months after exposure; more rapid disease progression in young and/or immunocompromised children
Nutritional status	Malnutrition associated with development of TB disease
Socioeconomic status	Linked to multiple other risk factors, including crowding, poor ventilation, food insecurity (malnutrition), as well as indoor and outdoor air pollution
Biomarker signatures	Promising early work on biomarker signatures, mainly in adults, that can be associated with the development of future TB disease, but none yet available

HIV: human immunodeficiency virus.
ART: antiretroviral therapy.

air pollution, limited windows) to be a reliable predictor of ten-year risk for developing TB in adults [43]. An additional major risk factor is time elapsed since TB infection (or re-infection). In children, most TB disease occurs within 12 months of primary TB infection [44], but the risk posed by re-infection, which maybe a common occurrence in TB endemic areas, is poorly characterized in the absence of a test for re-infection. This is one reason why household contacts are considered a high-risk group, given their recent TB exposure with likely TB infection/re-infection.

Although these factors are helpful, a more accurate method of predicting risk of future disease progression remains a major research gap. Exciting scientific work is currently underway looking at predictive biomarkers [45]. Some of the more advanced tests for predicting TB progression after infection include a 16-gene transcriptomic RNA signature [46]; immune activation-based tests [47]; peripheral blood monocyte/lymphocyte ratios [48]; and *MTB* antigens, such as the 'latency antigen' heparin-binding hemagglutinin [49]. While many of these tests appear promising and likely able to meet the WHO target product profiles, there are limited data in children and they remain a long way from being simple point-of-care tests used in clinical practice [50].

IMPLEMENTING TREATMENT OF INFECTION

Overall approach

The clinical decision to offer treatment of TB infection should be based on a balance of risk-benefit to both the individual as well as the community. The WHO recommends a different post-exposure management strategy for low- and high-burden countries, a seeming contradiction in a human-rights based approach to TB [51]. Treatment of TB infection is recommended for all household TB contacts in low-burden (i.e. higher income countries), whereas in high-burden (i.e. lower income countries) treatment of infection is recommended for children under five years and people living with HIV. This approach seems counter-intuitive considering that communities in high burden countries may be at higher risk for TB exposure (for example related to overcrowding) as well as at higher risk of developing TB disease due to factors such as

malnutrition and socioeconomic deprivation. Limiting preventive treatment to those under five and with HIV excludes other vulnerable groups including adolescents [52], children with poor nutrition and other immunocompromising conditions as well as children who have ongoing close household exposure (e.g. where there is a caregiver who has cavitory, smear-positive disease).

Therapeutic options for drug-susceptible TB infection

The various therapeutic options for treatment of TB infection are summarized in Table 3. Isoniazid treatment of infection has been found in systematic reviews to reduce the risk of TB by up to 64% in patients with HIV who have a positive TST (relative risk 0.36; 95% confidence interval (CI) 0.22–0.61) [53], and has been shown to reduce mortality [54]. Paediatric-specific randomized control studies have found a decrease in incidence of TB (hazard ratio 0.28, 95% CI: 0.10–0.78, $P = 0.005$) as well as reduction of mortality (8% compared to 16%: hazard ratio 0.46, 95% CI: 0.22–0.95, $P = 0.015$) in children receiving isoniazid compared with placebo [55].

Although there have been no head-to-head comparisons of the efficacy of six months versus nine months of isoniazid, re-analysis of past isoniazid trials suggests there may be a minor incremental benefit when isoniazid is given for up to nine months [56]. However, the increased duration may contribute to side effects and poor rates of treatment completion. In addition to isoniazid mono-therapy, the following regimens have also been shown to be effective in the treatment of TB infection and are currently favoured in most settings, except in children with HIV co-infection where drug-drug interactions between antiretroviral therapy (ART) and rifamycins is a concern:

- (1) Rifampicin plus isoniazid daily for three months: this regimen demonstrated similar efficacy and safety than nine months of isoniazid in children; with superior treatment adherence in the shorter combination regimen [57]. This therapeutic option is both endorsed by the WHO and available in a dispersible fixed dose combination tablet. Access in the past has been a challenge for many developing countries, however this is changing as this child-friendly combination tablet is now widely available through the Global Drug Facility [58] and its uptake should be encouraged.
- (2) Rifapentine and isoniazid given weekly for 12 weeks (i.e. three months, known as "3HP"): this regimen was found to be non-inferior when compared to nine months of isoniazid [59]. In this trial rates of treatment interruption due to adverse events was slightly higher in the combined therapy group (4.9% compared with 3.7% $P < 0.001$), however hepatotoxicity was less (0.4% compared to 2.7% ($P < 0.001$)) in the combination-therapy group. Completion rates were 82.1% in the combination group compared with only 69.0% in the isoniazid group [59]. Unfortunately, this study only included children above the age of two due to a lack of rifapentine pharmacokinetic data in younger children [60,61]. It is disappointing that this research work was conducted in 2011, yet rifapentine pharmacokinetic studies in children under the age of two are still pending, particularly considering that this is the highest risk group for developing TB disease who stand to benefit the most from this treatment option.
- (3) Rifampicin given daily for four months: this regimen has been shown to be non-inferior to nine months of daily isoniazid in a randomized clinical trial [62,63]. Systematic reviews have also shown rifampicin monotherapy for four months to be of a similar efficacy compared to isoniazid therapy; and with lower risk of hepatotoxicity [64].

Table 3
Treatment regimens for drug-susceptible and drug-resistant TB infection.

Regimen	Benefits	Limitations	Comment
<i>Drug-sensitive tuberculosis</i>			
6–9 months of isoniazid	Single drug; multiple studies show benefit; no drug–drug interaction with ART	Prolonged course of treatment, adverse events associated with isoniazid	Historical 'standard of care'
4 months of rifampicin	Single drug, shorter duration; large trial in children demonstrates safety and non-inferiority to 9 months of isoniazid	Difficulty obtaining non-combination tablets of rifampicin; drug–drug interaction with ART	
3 months of isoniazid and rifampicin	Shorter regimen; demonstrates non-inferiority to 9 months of isoniazid but safer and shorter duration; available as a child-friendly water dispersible combination tablet	Drug–drug interaction with ART	
3 months of once weekly isoniazid and rifapentine	Shorter regimen; demonstrates non-inferiority to 9 months of isoniazid, but safer	Optimal dosing of rifapentine not yet established in children <2 years; no paediatric formulations of rifapentine; high costs; drug–drug interaction with ART	Ongoing trial in adults (WHIP3TB) to assess if cycled courses are more effective than a single course
1 month of daily isoniazid and rifapentine	Shorter regimen; demonstrates non-inferiority to 9 months of isoniazid, but safer	As above; no studies in children or HIV-negative individuals	Paediatric application uncertain
<i>Rifampicin resistant/multi-drug resistant tuberculosis</i>			
6 months high-dose isoniazid (15–20 mg/kg/day)	May still work against strains with <i>inhA</i> mutations and low-level isoniazid resistance	Only assessed in retrospective observational cohort study	Potentially better than nothing
6 months fluoroquinolone monotherapy	Regimen appears safe; small cohorts and meta-analysis suggests regimen is effective; levofloxacin paediatric formulation available	Randomized trial data pending (V-QUIN study, TB-CHAMP study); likely not effective against fluoroquinolone-resistant strains of <i>MTB</i>	Levofloxacin is the most commonly used monotherapy
6 months fluoroquinolone combination	May provide broader coverage until drug-susceptibility test results become available	Multiple medications can cause additional side effects and adherence issues; high rates of resistance to ethambutol limit its added value	Should consider local drug resistance data
6 months of delamanid	Could be used for coverage of <i>MTB</i> strains that are resistant to the fluoroquinolones; delamanid safety established	Randomized trial data pending (PHOENIX); high cost; lack of access to paediatric formulation	Potential 'universal' preventive therapy option

ART: antiretroviral therapy.

HIV: human immunodeficiency virus.

MTB: mycobacterium tuberculosis.

- (4) Rifapentine and isoniazid given daily for one month (known as "1HP"): this regimen has been shown to be safe and in adolescents (≥ 13 years) and adults with HIV infection and non-inferior to nine months of daily isoniazid [65].

As mentioned before, a remaining challenge with rifamycin-based regimens in countries with high childhood HIV rates is that the rifamycins are powerful cytochrome P450 enzyme inducers. They therefore have drug–drug interactions with ART, especially with protease and integrase inhibitors. Paediatric dosing is not well established, but co-administration of the rifamycins and dolutegravir in persons living with HIV appears to be safe [66,67].

Therapeutic options for rifampicin-resistant TB infection

Treatment of TB infection saves lives and these benefits should apply to all forms of TB including rifampicin and multi-drug resistant TB (RR/MDR-TB). A 2017 meta-analysis found that persons with RR/MDR-TB exposure who received some form of treatment of infection (most commonly with fluoroquinolone-based treatment) had a 90% reduction in risk of developing TB. Preventative therapy was also considered to be cost-effective [68]. Assumptions that drug resistant *MTB* strains are either less virulent or less transmissible than drug susceptible forms of TB have been largely disproven, although strain-dependent heterogeneity is expected [69]. There are an estimated 19 million people with RR/MDR-TB

infection [70] and since the morbidity associated with RR/MDR-TB disease is far worse than for drug susceptible forms of TB the risk–benefit evaluation of RR/MDR-TB infection treatment seems even more favourable.

Data on the optimal treatment of infection with RR/MDR-TB is limited; available cohort studies report on fewer than 500 people globally [71]. Most studies used fluoroquinolone-based multi-drug regimens (with one or two other agents, including: high-dose isoniazid, ethionamide, ethambutol and/or pyrazinamide). Historically such multidrug regimens were used because of limited access to drug susceptibility tests (DST) – and thus an approach to treat more broadly with the hope that one of the drugs used would be effective. However, multidrug regimens increase the risk of adverse events and makes adherence challenging. There are currently two trials evaluating mono-therapy with levofloxacin (V-QUIN [ACTRN12616000215426] and TB-CHAMP [ISRCTN92634082]) and one with delamanid mono-therapy (PHOENIX [NCT03568383] [72]). Until the results of these trials are available, treatment of likely RR/MDR-TB infection should be offered based on drug susceptibility of the index patient [37].

Monitoring and evaluation of children receiving treatment of TB infection

Children receiving treatment of TB infection and their caregivers should receive counseling and support throughout treatment [73].

Table 4
Recommendations for action in prevention priority areas.

Prevention priority area	Actions for moving forward
<i>Finding children in need of TB prevention services</i>	Clinicians need to ensure that all children exposed to TB receive post exposure management. Assessment should take place at a convenient and private location that is easily accessible (in terms of location and hours) for the exposed individual. Programs and policy makers need to ensure there are adequate resources—both human and financial—to provide this crucial service. Research and innovation is needed to identify optimal care models, including qualitative studies on acceptability of different models of care for the persons receiving the services. Active case finding should extend beyond post exposure activities and should consider strategies for integrating TB prevention and case finding within community models, child health services and schools. Research is needed on the optimal way to identify children infected with TB outside of the household setting
<i>Detecting TB infection</i>	Priorities should include developing more reliable tests of infection that function well in high-risk children, are affordable and readily accessible. In the interim, health services should focus on using the most context and case appropriate approach to identify TB infection (i.e. exposure history or scores, currently available tests of infection)
<i>Identifying children at high risk of disease progression</i>	Priorities should include intensified prevention efforts among populations already known to be at risk for TB disease following infection (i.e. younger children, immunocompromised children) and research on biomarkers that can be used to predict the development of future disease
<i>Implementing treatment of TB infection</i>	Priorities should include on-going research into effective, short treatment of infection regimens – and making drugs (e.g. rifapentine) available at an affordable price. Urgent pharmacokinetic studies are needed on rifapentine dosing in children <2 years. More research on optimal preventive treatment of people with likely RR/MDR-TB infection - in the interim, levofloxacin monotherapy should be strongly considered as an option. Broadening treatment of infection guidelines should be considered to minimize TB-associated morbidity and mortality and improve market-driven demand. If children are not treated for TB infection, close follow up should always be undertaken for at least 12 months
<i>Galvanizing stakeholders to support success</i>	Donor investment in TB prevention activities is an urgent priority. Training civil society on TB prevention in children, identifying key partners to include in TB prevention efforts, and advocating for prioritization of TB prevention in children is a main concern

TB: tuberculosis.

RR/MDR-TB: Rifampicin-resistant/multi-drug resistant tuberculosis.

This will not only allow them to have optimal adherence but will also allow providers to assess children for drug-related adverse effects, as well as the development of signs or symptoms that could signal breakthrough TB disease [74]. Ideally, children receiving treatment of TB infection should be clinically assessed on a monthly basis, but this could be done in the community by trained ancillary personnel in order to avoid placing an undue burden on families to attend clinics. Directly observed therapy is not necessary, but treatment literacy should be promoted and provided alongside socio-economic and nutritional support [75]. No routine laboratory testing is required and a simple symptom-guided approach is safe and feasible in most settings [76].

Monitoring and evaluation of children not receiving TB treatment of infection

Not all children who are exposed to and/or infected with TB will receive treatment. In the absence of infection treatment, such children must be followed closely to rapidly identify any who develop disease. Although there are no specific data to guide how frequently this should be done and for what time period, some experts suggest that a formal symptom screening and clinical assessment should be done every three months for at least one year [77].

GALVANIZING STAKEHOLDERS TO SUPPORT SUCCESS

The global response to the HIV epidemic was fueled by activists and communities affected by HIV. Despite TB being the biggest global infectious disease killer, and with more than 2 billion people infected with *MTB* [78], the lack of demand from communities and civil society for preventive efforts is disconcerting. Limited activism for better TB prevention underlies a major market failure, leading to limited therapeutic products which are only available from a small number of manufacturers at high prices [79], as well as the de-prioritization of TB prevention activities from ministries of health particularly in high burden countries. HIV activism has benefited from large donors and awareness created by high

profile public figures. In comparison to the HIV field, TB research has long suffered from limited resources and lack of innovation – partially because of a lack of interest from resource rich countries who themselves have reached near TB-elimination. Broadening guidelines for all high risks groups could represent an opportunity to cultivate market demand and research.

CONCLUSIONS

Global efforts to eliminate TB have brought renewed attention to TB prevention. It is concerning, however, that access to crucial TB prevention services are not expanding globally [80]. There is thus an urgent need to re-commit to TB prevention, and since children are a vulnerable population for both TB infection and disease, efforts and resources should be preferentially targeted towards them. This paper has focused on challenges and progress in the TB prevention cascade, including identifying children in need of TB preventive efforts; screening for TB infection; predicting risk for progression from infection to TB disease; treating TB infection; and mobilizing civil society and other stakeholders to join and monitor progress related to preventing TB in children. There is a need to both rapidly deploy existing TB prevention technology as well as to improve upon that technology. In spite of the seeming difficulties in doing so—including a lack of both human and financial resources dedicated to preventing TB in children—there is both a moral and clinical imperative. After decades of failing to meet the needs of children when it comes to TB this is the very least of our child health obligations.

DIRECTIONS FOR FUTURE RESEARCH

Research and innovation is needed to develop optimal strategies and care models for finding, assessing and managing children who may benefit from TB prevention, including those infected outside the household. Reliable point of care test that are affordable and sufficiently sensitive in high-risk children should be a research priority, as is the use of biomarkers to accurately predict which children infected with TB are at risk of progressing to disease.

Another priority includes on-going research into effective, short and affordable treatment of infection regimens, as well as research on optimal preventive treatment of people with likely RR/MDR-TB infection. Urgent pharmacokinetic studies are needed on rifapentine dosing in children <2 years of age.

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