Getting it right for children: improving tuberculosis treatment access and new treatment options

EXPERT REVIEWS

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Children were often the forgotten victims of the global tuberculosis (TB) epidemic, neglected by traditional TB services as well as maternal and child health initiatives. Luckily this is changing with a greater focus on children and the issues regarding their optimal management. A common misconception is that children with TB are always difficult to diagnose and treat. New diagnostic tools are urgently needed, but most children with TB in high-burden settings can be diagnosed with available approaches and treatment outcomes are generally excellent. Increased TB awareness, appropriate training of health care workers and inclusion in integrated management of childhood illness strategies will improve the access and quality of care that children receive. This review highlights what needs to be done to ensure that no child unnecessarily dies from TB and provides a brief overview of new advances in the field.

Background

The impact of tuberculosis (TB) on child health has long been overlooked, and this blind spot has left millions of children at risk of preventable disease and death [1]. While much of the literature has focused on the problems with preventing, diagnosing and treating children with TB, few interventions have been implemented or tested in the field to reduce the detrimental impact of TB on the lives and health of children in TB-endemic areas around the world. We review the current state of TB services for children, including diagnosis, prevention and treatment, as well as recording and reporting. Based on this review, we then suggest some strategic interventions that – if rapidly implemented – could offer hope to children around the world, particularly in TB-endemic areas. The review considers interventions for children along the TB disease spectrum, from TB exposure and infection to those who become sick with the disease. Interventions at each of these time points offer opportunities to improve the health

outcomes of children. New advances in TB treatment and options of children are also briefly reviewed.

Precise numbers of children with active TB disease have remained elusive, and for many years the numbers of children with TB were not reported. Since 2012, the WHO includes estimates of the active TB disease burden in children in their annual global TB report, with an estimated 550,000 TB cases and 80,000 TB-related deaths (excluding deaths in HIV patients) [2]. It is estimated that 75% of these cases occur in the 22 high-burden countries. A recent study [3] suggested that in the 22 high-burden countries, more than 650,000 children developed TB in 2010, while 7.6 million became infected with *Mycobacterium tuberculosis*. Alternative global estimates suggest that up to a million children develop TB every a year, with the proportion of children who develop drug-resistant TB dependent on drug-resistance rates among infectious adult cases [4]. In addition to the high numbers of children thought to develop TB, there are also more than 53 million children estimated to harbor latent TB

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infection [3]. These numbers show that children who are currently treated for TB represent only 'the tip of the iceberg'. There is a need for more accurate and timely reporting of TB in children and improved service delivery to children with TB.

TB care as part of general pediatric programs

TB has historically been managed as a vertical program, separate to other areas of health care. The dangers of this approach have been highlighted with the emergence of the TB/HIV epidemic. With pediatric TB, poor integration of TB services and other areas of child health also present a major barrier to care. Children with TB routinely present to child-focused health services, such as maternal and child health (MCH) programs, vaccination, malnutrition and general pediatric services. However, TB programs are in the best position to identify child contacts of infectious adult cases. Both TB and child health services need to recognize children suspected of having TB and close contacts of infectious source cases to commence the right treatment, either for latent or for active TB, which will go a long way in reducing the morbidity and mortality associated with TB in children. A recent roadmap for childhood TB [5] framed childhood TB in the context of child survival. The roadmap provides a strong rationale for better integration of TB and child health services, but it is important that it is followed up with actual implementation and practical examples of how this happens in reality.

A simple way to start to bring MCH services and TB services closer together might be the introduction of universal screening questions for children and caregivers in TB-endemic areas, such as 'Has anyone in your family ever had TB?', or 'Does anyone in the family currently have a chronic cough?'. Within the TB programs, a simple question of 'How many children less than 5 years of age are in your household' for any person diagnosed with TB would go a long way in raising awareness around the need to identify and treat vulnerable young children. It is important that integration is not delayed by extensive and burdensome procedures on busy areas of clinical care. Better integration of these services will not only ensure that more children have TB prevented or diagnosed and treated, but it will also ensure that these children are recorded and reported so that the true extent of the burden of disease is revealed. As well as contributing to the global disease burden data, these numbers are important for targeting interventions, measuring success and securing funding.

Prevention of TB

Although accurate estimates are lacking, indications are that many children are exposed to TB every year. The 2014 global TB report estimated that 9 million adults developed TB in 2013 [2] and it is likely that at least 8 million young children have been exposed and are likely to have been infected [3,6,7].

Current vaccine-based strategies are dependent on *Bacille Calmette–Guérin* (BCG) vaccination at birth, which offers some protection, about 60–80% against disseminated forms of disease in young children, but fails to protect against future adult-type

disease and ongoing TB transmission within the community [8]. BCG is contraindicated in immunocompromised infants and children, including those with known HIV or high risk of HIV, because of the potential of developing disseminated BCG disease [9] Most high TB-burden countries provide BCG at birth or soon after birth, at which point in the majority of newborns, HIV infection cannot be confirmed; in these situations, unless there is access to rapid early infant diagnosis of HIV or the HIV-exposed newborn is clinically showing signs of immunosuppression, BCG should be given [10]. Identifying novel TB vaccines with enhanced protection in young children has proven elusive [11]; revised strategies now focus mainly on vaccination of adolescent and adult populations [12]. Although the protection provided by BCG plays an important role in the prevention of TB meningitis and other severe forms of TB [13], it alone cannot prevent TB in exposed children. Several preventive chemotherapy strategies have been shown to be beneficial in preventing progression to active TB disease among vulnerable children exposed to an infectious source case [14].

The most important preventive strategy is household contact investigation (also called 'contact tracing' in some settings), which facilitates rapid identification of all sick contacts and allows for preventive therapy to be started in the young and vulnerable. Isoniazid preventative therapy (IPT) has been shown to be effective in preventing drug-susceptible TB (DSTB), and there are a number of alternative regimens that could be used in children (TABLE 1) [15–17]. Most adverse events in children taking latent TB treatment involve nonspecific gastro-intestinal complaints and mild transient elevation of liver enzymes with minimal risk of severe hepatotoxicity. Screening for IPT can be done at the lowest level of health care facilities using symptoms alone [18]; predictive score charts have been developed for prioritizing TB contacts [19]. In addition to treating those with or at risk of latent TB, IPT is indicated for all young children (<5 years) and HIV-infected children of any age in close contact with a sputum smear-positive TB case, AND not having any evidence of active TB disease. Preventive therapy needs to be given for the full duration of the treatment specified and programs need to support activities for adherence of IPT. Observational studies evaluating a three-drug quinolone-based multidrug-resistant TB (MDR-TB) preventive therapy regimen in vulnerable pediatric contacts of infectious patients with MDR-TB demonstrated benefit [20] and formal randomized controlled trials using quinolone monotherapy are in progress. With adequate training and pragmatic implementation of household interventions, large gains in preventing future morbidity and mortality can be made as well as potential cost savings [21].

Diagnosing TB in children

There is a perception that diagnosis of TB in children is difficult, but in fact making a clinical diagnosis in children is relatively straightforward as long as the index of suspicion is high, appropriate questions are asked (such as symptoms of TB and history of contact with TB patient), the clinical examination is done well

Table 1. TB preventive therapy options in children exposed to infectious cases with drug-susceptible TB [15–17].

Regimen	Dose	Age group	Comments
6–9 months INH monotherapy	10 mg/kg daily (7–15 mg/kg) Maximum dose: 300 mg	All	Most experience with this regimen; length of treatment pose adherence problems
12 doses of weekly INH and RPT[†]	INH: 15 mg/kg; 900 mg maximum RPT: 10.0–14.0 kg 300 mg 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg Maximum dose: 900 mg	2 years and over Not recommended if under 2 years	Strong clinical trial results but limited field experience; requires DOT
4 months RMP[†] monotherapy	15 mg/kg (10–20 mg/kg) Maximum dose: 600 mg	All	Use when INH not tolerated or with known INH monoresistance
3 months of INH and RMP	INH and RMP doses as above; often used as single dissolvable fixed-dose combination tablet	All	Good experience in the field, but limited use in TB-endemic countries

[†]Rifamycin (RMP and RPT)-containing regimens can interfere with antiretroviral treatment.
DOT: Directly observed therapy; INH: Isoniazid; RMP: Rifampicin; RPT: Rifapentine; TB: Tuberculosis.

and other differential diagnoses are accurately excluded. The challenging element in TB diagnosis in children is often bacteriological confirmation of the clinical diagnosis. TB can present in children of any age, but in endemic countries it is more likely to be in the under-5 age group. The spectrum of disease is different from adults, with children having a higher rate of extrapulmonary TB [5]. The very young (<2–3 years of age) often present with disseminated disease, whereas adolescents are more likely to present with adult-type pulmonary disease.

Young children often present with nonspecific symptoms. The wide range of clinical presentations requires a high index of suspicion to ensure that the diagnosis is not missed. While tuberculin skin testing can be used to support the diagnosis of TB, it is not very specific and too insensitive to be used as a 'rule-out' test. In TB-endemic countries, its use is restricted by its inability to distinguish between latent and active disease and the rates of false positive/negative results, especially in HIV-infected and malnourished children. Interferon-δ release assays do not offer major advantages over tuberculin skin testing in terms of sensitivity and specificity [22] and the WHO advises against their use in middle- and low-income countries [23].

There are a range of other screening tools, particularly 'score charts', that have been developed to aid the diagnosis of TB in children [24]. Unfortunately, none of these have been validated and are hampered by the nonspecific and variable symptoms with which active TB disease may present in children. These scoring systems tend to focus on duration of illness, history of TB contact, tuberculin skin test result, nutritional status and presence of constitutional symptoms of TB, but their performance is highly variable in different settings and with different disease manifestations, as such there is no recommendation regarding their use [9]. The fact that the clinical picture of TB in younger children overlaps significantly with other common childhood illnesses, such as severe acute malnutrition, respiratory tract infections, AIDS-associated opportunistic infections and a lack of an easy confirmatory or 'rule-out' test, highlights the importance of appropriate clinical follow-up to ensure clinical recovery if active TB disease is not considered likely. The WHO recommends that TB diagnosis should be based on careful history, clinical examination, tuberculin skin testing and, wherever possible, bacterial confirmation [9]. Some practical approaches to diagnosing TB in children [25] are highlighted in TABLE 2.

Bacteriological confirmation presents challenges in children suspected of having TB, but can often be achieved [26,27]. Although sputum is the most common specimen collected, other sampling strategies are available (TABLE 2). Once a sample has been obtained, there are a variety of different diagnostic tests that can be performed, including smear microscopy, solid and liquid culture and molecular tests such as the XpertMTB/RIF [28]. Optimal use of these tests has been reviewed in recently updated guidelines [9]. Molecular tests, like XpertMTB/RIF, also have a role to play in extra-pulmonary TB [29]. Updated consensus case definitions for TB diagnostic studies in children are expected in 2015 [30], which should assist testing of novel diagnostic options. The most important step for diagnosing children is to suspect TB disease in those with risk factors (i.e., exposure in a household setting, HIV disease) or chronic illness (weight loss, failure to gain weight, fever, listlessness) not responsive to first-line treatment. Although bacteriologic confirmation is ideal, especially for children at risk of MDR-TB, this should not deter or unnecessarily delay treatment initiation.

Treatment of DSTB

Children have excellent TB treatment outcomes if diagnosed early [31], with minimal adverse effects. The treatment of

Table 2. Overview of specimen collection methods [71].

Specimen collection method	Description and characteristics
Gastric aspiration	Nasogastric tube inserted down the throat into the stomach to extract sputum • Difficult and fairly invasive procedure (variable cultural acceptance) • Requires hospitalization or repeated visits on three consecutive days • Must be performed by trained nurses • Highly uncomfortable for children; poorly accepted
Nasopharyngeal aspiration	Tube inserted through nose to suction secretions at the back of the throat • Relatively noninvasive • Variable performance, but some studies suggest similar yield to culture of sputum induction • Not yet widely used; more data needed[†] to assess usefulness of samples obtained
Sputum induction	Child breathes into bronchodilator containing gases which irritate lungs and induce coughing • Can be performed on most children and is safe. Requires some basic equipment and infection control measures • Requires trained nurses. Highly operator dependent • One sputum induction provides same yield of bacteriological confirmation as three gastric aspirations in hospitalized children; incremental yield with a second sputum induction • Useful in hospital settings; limited data currently available on the use of this method in primary health care facilities
Acoustic sound wave sputum induction (i.e., lung flute®)[†]	Handheld device that sends sound waves into the lungs when patient exhales, thus loosening secretions and improving sputum expectoration • Can be performed on young children • Noninvasive • Takes 20–25 min to collect • Minimal studies in TB patients • More data needed to assess clinical utility and potential transmission risks
String test	Child swallows gelatin capsule containing coiled nylon string, capsule recovered later by pulling string • More appropriate for older children, who tolerate procedure well • Yield of bacteriological confirmation similar to sputum induction in HIV-infected adult population [73] • Limited by cost, lack of widespread availability • Younger children have difficulty swallowing the capsule • Not yet widely used; additional studies needed
Stool	• Easily obtained; can be done at primary health facilities • Contains TB bacteria from swallowed secretions • Specimen requires stringent decontamination procedures; thus culture from stool specimens has proven insensitive so far • More studies needed to assess usefulness, feasibility
Lymph node FNAB	Performed as a needle biopsy (not an aspirate) with a fine 22-gauge needle [72] • Minimally invasive • Can be safely performed on outpatient basis • Yields specimens suitable for smear microscopy, culture and drug-sensitivity testing • Yield for bacteriological culture (to confirm TB diagnosis) might be higher than with sputum • Potentially underutilized diagnostic option
Other site-specific methods	• Lumbar puncture, pleural fluid or pericardial tap, and so on. • Sample depending on likely source

[†]See reference [73].
FNAB: Fine-needle aspiration biopsy; TB: Tuberculosis.

Table 3. Recommended daily doses of first-line tuberculosis drugs in children [9].

Anti-tuberculosis drug	Dose and range (mg/kg)[†]	Maximum dose (mg)	Side effects of note[‡]
Isoniazid	10 (7–15)	300	Peripheral neuropathy, hepatoxicity
Rifampicin	15 (10–20)	600	Hepatoxicity, color secretions orange
Pyrazinamide	35 (30–40)	2000	Hepatotoxicty
Ethambutol	20 (15–25)	1200	Optic neuritis

[†]Normal adult doses advised for children who weigh more than 25 kg.
[‡]Children generally tolerate these medications well, although mild gastrointestinal upset, transient rise in liver enzymes without clinical symptoms or jaundice are not uncommon.

DSTB in children follows the same principles as in adults using a 2-month intensive phase (isoniazid, rifampicin, pyrazinamide ± ethambutol) and two drugs (rifampicin and isoniazid) during the 4-month continuation phase. However, the recommended drug doses were revised upward in 2010 [32], particularly in children weighing less than 25 kg (TABLE 3) due to new evidence showing that the previous doses did not achieve adequate serum levels [9] with pharmacokinetic (PK) data collected in different age bands [33–36]. Unfortunately, this meant that the current fixed-dose combination (FDC) tablets for the treatment of DSTB in children are no longer appropriate. There have been interim guidelines [37] on how to prescribe the current FDC to achieve optimal doses while new FDCs compatible with the revised dosage recommendations are produced, but it is unclear how widely these have been used and if in fact the new dosages have been widely implemented [38]. The new quality-assured FDC is expected to be available through the Global Drug Facility in 2015, with wider availability by 2016.

FDC is recommended for the treatment of children [9] but despite this recommendation, national programs have been slow to implement, with a recent report showing that out of a survey of eight countries, only two recommended the use of FDCs for the treatment of DSTB in children [39].

It is particularly important that when the new quality assured FDC in line with the new dosages recommendations is available, it is quickly incorporated into national guidelines and its uptake promoted. This will ensure that children receive the correct drug dosages and reduce the pill burden for children, especially those co-infected with HIV. The new product should ideally be made available through TB programs and MCH services, as this is where a substantial number of patients will present. Appropriate training should be made available to MCH services to not only suspect and test for TB, but also to ensure that they can prescribe and treat TB with the appropriate TB medications, so that children are not lost in referral to TB services, and there is a genuine 'one-stop' service for children presenting to MCH services with TB.

Other recent changes in the pediatric guidelines include clarification of the use of ethambutol and streptomycin. Ethambutol does not have to be used in children with pauci-bacillary disease who live in settings with low HIV prevalence or low prevalence of isoniazid resistance and are HIV negative. They can be treated with a three-drug regimen, isoniazid, rifampicin

and pyrazinamide (HRZ), for 2 months followed by a two-drug (HR) regimen for 4 months. Ethambutol is recommended for inclusion in the intensive phase of treatment in areas with high rates of isoniazid resistance (as defined by local programs; mostly considered if isoniazid resistance rates rate exceeds 20% in treatment-naïve adults) [9], in HIV-infected or otherwise immunocompromised children and in those with extensive disease. The role of the fourth drug in the intensive phase is considered important to improve outcomes in the presence of a large microbial load and to reduce the risk of developing drug-resistance; its benefit in pauci-bacillary disease is likely to be limited. Previous concern regarding ethambutol use is the rare side effect of irreversible blindness, especially in young children unable to report visual acuity changes, but this risk is minimal at currently recommended dosages [40,41], Streptomycin is not recommended for use in any first-line treatment regimen for children (TABLE 4). There are new efforts to assess the possibility of decreasing the duration of treatment in select patient groups. The shorter treatment for minimal TB in children (SHINE) trial aims to evaluate the efficacy of 4 versus 6 months TB treatment in children with minimal disease using new WHO-recommended dosages of first-line TB drugs: it will commence in 2015 [42].

Drug-resistant TB

Although there are no official numbers for children with MDR-TB, recent modeling work estimated that there were likely to be more than 30,000 cases of MDR-TB in children in 2010 [4], yet there are less than 500 reported in medical literature [43] The challenges regarding confirming the diagnosis are the same as TB in general in children, starting with the difficulties of getting adequate samples for culture and drug susceptibility testing. Adequate history taking and knowing the resistance pattern of any close contacts with TB is key to ensuring that the risk of MDR-TB is considered.

There is little evidence to guide optimal MDR-TB treatment in children, with the current recommendations based on extrapolations from adult recommendations and expert opinion [44]. Currently, the recommendations are based on the similar strategies used in adults – an intensive phase including at least four second-line drugs likely to be effective, (in the case of children with no confirmed resistance pattern, use resistance pattern of likely source case) and to include an injectable agent,

Table 4. WHO recommended regimens for the treatment of drug-susceptible TB in children [9][†].

Regimen	Epidemiological setting and TB disease manifestation
2 months HRZ/4 months HR	Regions of low HIV prevalence/HIV-negative children and low background isoniazid resistance AND • Smear negative pulmonary TB • Lymph node TB • TB peripheral lymphadenitis
2 months HRZE/4 months HR	Regions of low HIV prevalence/HIV-negative children and low background isoniazid resistance AND • Smear positive pulmonary TB • Extensive pulmonary disease • Severe forms of extrapulmonary disease (excluding TB meningitis or osteoarticular TB) OR Regions of high HIV prevalence or high background resistance of INH or both • All forms of pulmonary TB (smear –ve and smear +ve) • All forms of extrapulmonary disease (excluding TB meningitis or osteoarticular TB)
2 months HRZE/10 months HR	TB meningitis or osteoarticular TB

†Streptomycin and use of the re-treatment regimen (Category 2) is not indicated in children.
E: Ethambutol; H: Isoniazid; R: Rifampicin; TB: Tuberculosis; Z: Pyrazinamide.

a fluoroquinolone and pyrazinamide. Children do far better on MDR-TB treatment than adults and have fewer side effects, but hearing loss is a significant concern with the prolonged use of an injectable agent [43,45]. Although adult recommendations are for 8 months of an injectable agent, 4–6 months may be adequate in young children, especially in those with limited disease [43]. The total treatment duration may also be shortened to 12–18 months in this select group [46]. An additional challenge of treating children with MDR-TB is the lack of pediatric appropriate mediations. Of the drugs currently used to treat MDR-TB, only six have a pediatric preparation (TABLE 5).

There is an urgent need for pediatric drug formulations, but the development of these products is hampered by the lack of PK data on the exact doses required for second- and third-line drugs. Recently published data showed that children may require higher doses than currently recommended for moxifloxacin [47] and lower doses of kanamycin and amikacin [48] and there are additional studies currently looking at the PK and safety of routine second-line drugs used in MDR-TB [47]. These will hopefully answer the questions regarding exact dosing schedules, allowing more detailed guidelines for children and the development of pediatric appropriate formulations. The Sentinel project on Pediatric Drug Resistant TB, a global network of experts and pediatric MDR-TB treatment providers have developed a field guide [49] on the management of MDR-TB in children that provides practical guidance.

For adult TB, two new drugs have been developed and recommended for the use in MDR-TB, bedaquiline [50] (Janssen) and delamanid [51] (Otsuka). Despite being registered for over a year, these two drugs have only been used in compassionate use or equivalent programs. Delamanid has been given to a child under 10 years [52] and bedaquiline to adolescents [53] as part of compassionate use programs. Due to the lack of pediatric data, they are not recommended for use in children by the regulators or the WHO. Only delamanid has started a pediatric trial [54] to evaluate the PK, safety, tolerability and antimycobacterial activity of delamanid in combination with MDR-TB therapy for HIV-infected and -uninfected children and adolescents. The design of this trial allows for the inclusion of children with 'probable' TB and may better reflect the reality of clinical practice than results from studies only including children with bacteriologically confirmed disease [55]. This shows that pediatric trials of new products can be started in parallel to the ongoing trials for the adult product. The early commencement of parallel pediatric studies should become the norm for all new product and regimen trials. Bedaquiline has a pediatric trial in planning and pediatric formulations of both these products are being produced. New TB drugs in Phase II development include pretomanid (Global TB Alliance), sutezolid (Sequella) and AZD 5847 (Astra-Zeneca). As far as we are aware, pretomanid is the only one that has a planned pediatric formulation, but has yet to initiate pediatric studies.

The lack of access to the new drugs for children is symptomatic of a broader

Table 5. Available pediatric formulations to treat MDR-TB [74].

Second-line drugs	Third-line drugs
• Amikacin (IV 100 mg vials) • Levofloxacin[†] • Para-aminosalicylate sodium(PAS)(dosage spoon)	• Isoniazid • Amoxicillin/clavulanic acid • Linezolid
3 out of 10 SLD	3 out of 5 TLD

†Levofloxacin oral solution: not recommended in children <3 years and composition not necessarily adapted for long-term use.
SLD: Second-line drugs; TLD: Third-line drugs.

Table 6. Pediatric trials for treatment of drug-susceptible or drug-resistant TB in children [75].

Trial name	Status	Criteria
232 PK and safety of delamanid, OBR for treatment of MDR-TB	Enrolling; primary results expected 2016	HIV-negative children 6–17 years old with MDR-TB
233 6 months of delamanid, OBR for treatment of MDR-TB	Enrolling; primary results expected 2017	HIV-negative children 6–17 years old with MDR-TB [children <5 years old will get pediatric formulation]
IMPAACT 1108 PK and safety of bedaquiline, OBR for treatment of MDR-TB	Planned; opening 2015	HIV-negative children 0–18 years. old, HIV-positive children 12–18 years old with MDR-TB [children <12 years]
SHINE 4 vs 6 months using 2010 WHO dosing guideline–adjusted FLD fixed-dose combinations for treatment of minimal TB	Planned; opening 2015	HIV-positive or -negative infants, children and adolescents with minimal TB
PATCH Safety and efficacy of levofloxacin and rifampin for treatment of TB meningitis	Planned	HIV-positive or -negative infants and children with drug-susceptible-TB meningitis
MDR-PK PK and safety of SLDs for treatment of MDR-TB	Enrolling; interim results presented 2013; final results expected 2016	HIV-positive or -negative infants, children and adolescents with MDR-TB or LTBI

FLD: First-line drug; LTBI: Latent *M. tuberculosis* infection; MDR: Multidrug resistant; OBR: Optimized background regimen; PK: Pharmacokinetic; SLD: Second-line drugs; TB: Tuberculosis.

exclusion of children in advances in TB care. Children have been excluded from clinical trials and observational trials in all areas of TB – Xpert MTB/RIF was developed and recommended for use in adults before pediatric trials were commenced and recent trials into shortened regimens for both DSTB and MDR-TB do not have a pediatric component [56,57]. Current pediatric TB trials involving new and current MDR-TB drugs as well as new regimens are summarized in TABLE 6. A number of consensus documents outlining ways to facilitate the inclusion of children in TB trials, both for new drug and diagnostic [30] development, have been developed and outline clear steps to be taken in this regard. These include early safety and PK studies in pediatric populations once efficacy has been proven in adults and a requirement for pediatric development plans for new drugs as per the EMA regulations [58].

TB/HIV co-infection
Children who are co-infected with HIV represent a very important group, but efforts to characterize the burden are hampered by a lack of data on the incidence of TB among HIV-positive children and the prevalence of HIV among children diagnosed with TB [59]. Co-infected children are harder to diagnose, and it is recommended that all children living with HIV in a TB-endemic setting should be regularly screened for TB, ideally at every interaction with health care providers to ensure that TB diagnosis is not missed. Early diagnosis and prompt treatment initiation is essential in co-infected children, as children with HIV do not do as well as HIV-negative children, especially in

the first few months. TB has been reported to be the third most common cause of death in HIV-infected children with a clinical diagnosis of acute severe pneumonia [60]. Apart from being at increased risk of disease progression, co-infected children also have a short time period between becoming infected and presenting with symptoms; in infants this can be as short as 4–8 weeks, or even at birth in cases with congenital infection [61].

With regard to treating children co-infected with DSTB and HIV, standard treatment is recommended with consideration of an additional 6 months of isoniazid after treatment completion [9]. Early commencement of anti-retroviral treatment (if not already on them) is paramount, ideally within 2–8 weeks of TB treatment initiation. The use of FDCs should be encouraged where possible to minimize the pill burden.

TB & malnutrition
Nutritional status is another key co-morbidity that has a considerable effect on the outcomes of children with TB. Severe acute malnutrition, especially among under-5 children in developing countries, affects the immune status conferring a higher risk for TB infection and morbidity [62]. The addition of HIV co-infection in a malnourished child with TB confers a substantial risk of death [63], but the diagnosis is often not pursued. A recent study from India showed that nearly one-third of the children who reached nutritional feeding centers were not evaluated for TB, and among those evaluated, the diagnostic algorithm was not followed in two-thirds [64]. Pulmonary

TB may be a common cause of acute pneumonia in severely malnourished or HIV-infected children under 5 years of age [65]. In Bangladesh, 23% of children with severe acute malnutrition and respiratory symptoms or radiological pneumonia were started on TB treatment due to bacteriological or clinical diagnosis; the majority reported no known TB contact and were tuberculin skin test negative [66]. It is important to raise TB awareness in malnutrition programs, especially in children not responding to therapeutic feeding regimens.

Expert commentary

The burden of disease suffered by children and TB's contribution to HIV, malnutrition, pneumonia and meningitis-related morbidity and mortality in TB-endemic countries is finally being recognized. Since children mostly develop TB with 1 year of infection [67], they represent a marker of ongoing transmission and reflect the current TB control status within communities. Some of the 53 million children latently infected with TB [3] may also present as future cases. It is important to recognize that time and resources invested in providing TB services to children is a good investment to reduce child mortality, limit TB transmission and reduce future case numbers.

There are many potential priorities, but TB screening of vulnerable children and use of preventive therapy when required are key priorities, where major policy–practice gaps persist [68]. Pragmatic household interventions would facilitate active case finding, adequate use of preventive therapy and pro-active HIV testing where relevant. Children with HIV are at higher risk and should be prioritized for preventive therapy and actively screened for TB. Screening for TB on nutrition and pediatric wards should become standard practice as TB care becomes more integrated in child health services.

There are adequate guidelines and roadmaps, but it is essential that these documents are translated into action. This will require concerted effort by a range of stakeholders, including local governments and donor agencies. A sensitive point-of-care screening (rule-out) test and tools for improved diagnostic confirmation are urgently needed, but most children can be correctly diagnosed with existing approaches. With optimal sampling, the bacteriological yield would be increased if children had better access to Xpert MTB/RIF and *M. tuberculosis* culture. For maximum impact, countries need to ensure that there is access to and training for the full range of sample collection methods to optimize chances of bacteriologic confirmation. There are promising developments with exploration of highly sophisticated new diagnostic approaches [69,70], age-appropriate PK studies to establish optimal drug doses in

relevant age groups and inclusion of children in new TB treatment trials, including the treatment of MDR-TB.

No child should die from TB, since it is a preventable and treatable illness with excellent treatment outcomes if diagnosed early. Pediatric TB represents a spectrum with opportunities to intervene at multiple time points, to either prevent *M. tuberculosis* infection and progression to disease, or to treat active TB disease and minimize associated complications. We can do much better with the tools at our disposal, if national TB programs, MCH services, donors and international health agencies recognize the multiple benefits of optimizing TB care in children.

Five-year view

This is an exciting time in pediatric TB. There are a number of studies and tools that should further improve outcomes of children with TB. For DSTB, the arrival of the appropriate FDC in line with the increased dosages recommended in 2010 will enable easier prescribing of treatment and reduce the pill burden for children. For drug-resistant TB, the conclusion of PK studies for the current MDR-TB drugs will ensure that children receive the right doses and allow pediatric appropriate formulations to be produced. There should also be pediatric formulations and data available for new TB drugs.

Within 5 years, the study looking into shortening the regimen for DSTB should have concluded, and hopefully there will be pediatric arms incorporated into some of the MDR-TB trials looking at shortening and simplifying the regimen, especially dropping the injectable agent as an essential part of the regimen. In addition, we hope that some of the strategies outlined in the many documents relating to pediatric TB will have become a reality; improved sampling strategies, molecular or culture tests replacing smear, systematic use of dispersible FDCs for DSTB and pediatric formulations for second-line drugs.

Hopefully within the next 5 years, TB will be part of routine screening in all vulnerable children, sick children with suspicious symptoms and in every child with close TB contact. Improved delivery of TB services will reduce disease and death rates in children, particularly in TB-endemic areas, and have the added benefit of reducing future reactivation disease, particularly in non-endemic areas where transmission is well controlled.

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Key issues

- Diagnosing children with tuberculosis (TB) is relatively uncomplicated in most instances. Diagnostic algorithms should reflect this. Bacterial confirmation is more challenging, but is possible in most children if appropriate samples are obtained and tested (prioritizing culture over smear).
- Awaiting bacteriological confirmation should not unnecessarily delay treatment, especially in sick, HIV co-infected or malnourished children. Appropriate history taking and knowledge of the likely index case identify those at risk of drug-resistant forms of TB.
- Household contact screening and TB prevention should be better implemented, especially in TB-endemic areas where this is often not even attempted. Vaccine development should retain a strong focus on the protection of young and vulnerable children.
- Dissolvable fixed-dose combination tablets work well in children. New quality assured pediatric fixed-dose combinations, with optimal first-line drug ratios, are expected to be available in 2015. It is vital that this is taken up by country programs.
- HIV and nutritional screening is essential in all children diagnosed with TB, with appropriate integration of TB, HIV and other child health services.
- Young children usually have pauci-bacillary disease, which mean that they may be cured with shorter treatment regimens. This requires further evaluation.
- New drug and regimen trials should all have pediatric components, at least to assess safety and pharmacokinetic profiles in children and develop child-friendly formulations.
- Low- and middle-income countries need to invest more in child health, including the provision of TB care to children.

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