Childhood tuberculosis: a concern of the modern world

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Childhood tuberculosis is a potentially lethal disease, which is underdiagnosed and undertreated
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As childhood tuberculosis (TB) reflects recent transmission, its burden provides an accurate measure of the level of TB control achieved in a particular community. Moreover, infected children represent the main reservoir of *Mycobacterium tuberculosis* (MTB) as potential future cases. However, childhood TB is neglected by scientists, policy makers, healthcare professionals and product developers [1]. Moreover, the interests of individual patients and public health may be conflicting. As children are considered in the majority of cases as noncontagious, asymptomatic disease is frequently ignored [2]. This is why, in 2013, the World Health Organization (WHO) developed a roadmap aiming to achieve zero deaths due to childhood TB by 2025 [3]. This article aims to highlight the underestimated reality of childhood TB, emphasising improved diagnosis possibilities and new treatment modalities, and advocating for dedicated paediatric operational research and clinical trials.

Methods
Active scanning of the recent literature using the keywords: ''children tuberculosis'', ''latent tuberculosis infection'', ''new diagnosis tools'' and ''treatment modalities'' was performed using PubMed and EMBASE. In addition, International Union Against Tuberculosis and Lung Disease publications were screened and WHO policy and guidance documents on TB were obtained from the WHO website (http://www.who.int).

Epidemiology
Each year, more than 74 000 children die from TB [3]. Exposure to an adult with pulmonary TB was reported to increase mortality by 70% in children under 5 years of age in high-burden settings and by eight-fold when the mother had TB [4].

The global burden of childhood TB is under-reported due to paucibacillary disease and the difficulty of confirming the diagnosis. In China, the prevalence rates for bacteriologically positive pulmonary TB and smear-positive cases were eight and 13 times less than the clinically diagnosed pulmonary TB rate, respectively [5]. TB disease and latent TB infection (LTBI) frequencies in children are dramatically underestimated. According to national reports, childhood TB accounted for 3.5% of the global TB caseload

in high-burden countries, while best estimates suggest that 11% of TB cases occur in children, with 332 000 paediatric patients being undiagnosed or unreported [2, 6]. This data discrepancy also concerns Western Europe. An active surveillance system demonstrated an underestimation of childhood TB in the UK by about one-fifth [7]. The cumulative risk of infection in Greenland at 18 years of age was 13.4% [8].

Children's risk factors for infection are younger age, birth in a high prevalence country or foreign-born parents, HIV infection and prolonged close contact with the index case. Related index case risk factors are smoking, being a young adult, having cavitary lesions and a positive sputum smear test [9, 10]. Smear-negative and culture-positive patients, extrapulmonary TB cases and TB among schoolmates, while less contagious, also constitute a source of contamination [4, 6, 11–13]. The period of time in close contact with the TB patient is essential. When the index case was a teacher, the relative risk of exposed children, at school for >6 h per day, was approximately 30 [9, 14]. By contrast, a brief exposure to a highly infectious individual may result in a high risk for healthy children [15]. A contact-scoring tool estimated exposure quantification by considering maternal TB and sleep proximity, index case infectivity, duration of exposure and exposure to multiple index cases. It allowed detection of 80% of a child's risk of infection in a high-burden setting [16]. In South African townships the mean number of smear-positive adults per exposed child for uninfected children, latently infected children and TB cases was 1, 1.6 and 1.9, respectively [17]. The majority of childhood TB cases were diagnosed in the same year as an adult index case. However, more than 30% of the time the adult case was diagnosed later, demonstrating the ongoing contamination in the community [17]. In a high endemicity setting, exposure to a known TB case in the past 2 years did not increase TB risk, while biomass exposure was a significant risk factor [18]. In high-burden TB communities, the first infection occurs in childhood, but is not a single lifetime event [19].

Family clusters of TB cases are ascribed to genetic susceptibility. Within the same house, TB mortality risk was higher for children belonging to the index family than for children living there who were not related to the index [4]. In Greenland, annual risk of TB infection was independent of age and bacilli Calmette–Guérin (BCG) vaccination programme, but varied substantially by ethnicity [8].

Disease risk after primary infection with MTB is greatest in infants and declines to a nadir at age 5–10 years. In Western Europe more than half of children with TB are <5 years old [20]. Endogenous reactivation might account for the second peak of TB in adolescence [21, 22]. A temporal association has been reported between children's hospitalisations for TB, invasive pneumococcal diseases and influenza [23].

HIV infection has had a large impact on the epidemiology and severity of childhood TB [6]. In a prospective study conducted in the Western Cape, 23.4 cases of active TB were recorded per 100 HIV-infected children per year [24]. The high TB incidence among HIV-infected children is, in part, explained by increased risk of TB exposure [25]. The available epidemiological data for TB in childhood are summarised in table 1.

Natural history: LTBI and immunological data

Until recently, LTBI was supposed to precede TB disease, implying persistence of a low number of dormant mycobacteria in the organism. However, in numerous cases infection is a self-limited disease with no risk of progression [35]. In addition, in recently exposed children, the boundary line between primary TB and LTBI may be difficult to define [36]. Smear positivity in some asymptomatic and chest radiography-negative children further blurs the boundaries between infection and disease. The risk of progression to TB is highest after a median incubation period of 6 weeks [37]. The physical location of bacilli during latent infection remains poorly understood [35]. The persistent bacilli are thought to encounter constraining conditions that induce a distinct set of gene expression profiles and chromosomal mutations [38].

Innate immunity constitutes a strong line of defence against MTB. These innate response mechanisms may be powerful enough to prevent an adaptive specific response [39, 40]. The T-cell population, which is essential to overcome acute infection, is mainly made up of T-helper (Th)1, Th17, cytotoxic T-cells and regulatory T-cells [35]. Th1 differentiation is induced by interleukin (IL)-12 and IL-18. Th1 cells produce interferon (IFN)-γ, which in conjunction with tumour necrosis factor (TNF)-α activates macrophages and modulates granuloma constitution [39]. The balance of T-cell subpopulations at the level of the granuloma regulates protective immunity, inflammatory pathways and anti-inflammatory responses [35, 41]. B-cells are observed in significant numbers in granulomas, but their role remains undefined [40].

Secretion of IFN-γ by lymphocytes is a poor correlate of protection as it depends on the antigenic load [35]. *In vitro*, T-cells from infected children stimulated by mycobacterial antigens produce Th1 and Th2 cytokines with no differences between LTBI and TB disease cases [42]. The frequencies of MTB specific CD4, CD8 and $\gamma\delta$ T-cells in blood do not correlate with vaccination protection in 10-week-old children who have received routine infant vaccination [43].

TABLE 1 Childhood incidence of tuberculosis (TB) according to notified cases or case–control studies

Country	Year [ref.]	Incidence per 10^5 children	Origin	Confirmed TB	MDR-TB	<5 years of age	Extrapulmonary TB
Switzerland	1996–2011 [26]	1.6	Foreign born: 83	51.9	1.8	48	
Denmark	2000–2009 [27]	1.9	Foreign born: 79	50	0.3	33.7	23.5
Greenland	2010 [8]	180.0 (prevalence)	Inuits				
Spain	2005–2009 [28]	8.1	Foreign born: 25	51			16
England and Wales	1999–2006 [29]	4.3		27	2.3	31	40
London, UK	2006 [30]	13.3	White ethnic: 8.1 Black African: 53.5 Born in UK: 56	1			41
Washington, DC, USA	2007 [31]	1.9				49	
Japan	2011 [32]	0.50	Foreigners: 10			39.3	28.1
Rondona state, Brazil	2006 [33]	Global: 7.6 Indigenous: 311	Indigenous: 31.5			41	20
China[#]	2002–2010 [5]	91.8					
Township community, South Africa[¶]	2007 [17]	721		11.6			13
Zambia	2011 [34]	69		6	No data		

Data are presented as %, unless otherwise stated. MDR: multidrug-resistant. [#]: in China no decrease was observed between 1979 and 2000; [¶]: in South Africa incidence of smear-positive TB in children was 83 per 100 000 in townships versus a global incidence of 30 per 100 000 in South Africa.

Genetics

As discussed previously, IFN-γ and IL-12 are essential to defence against mycobacteria. Mendelian susceptibility to mycobacterial disease (MSMD) is a clinical syndrome that predisposes to infections caused by weakly virulent mycobacteria, such as BCG and by usual MTB strains [44]. Severe TB in conjunction with MSMD had been estimated to be present in between 5% and 40% of cases [44]. Several mutations in autosomal genes and genes within the X chromosome have been identified in MSMD, all of which affect the IL-12/IFN-γ pathway [43–47]. Consequently, IFN-γ has been reported to be partially effective for mycobacterial infection in IL-12 receptor β1-deficient patients [45, 48]. Genetic background also plays a role in tuberculin skin test (TST) responsiveness after BCG vaccination [49, 50].

Diagnosis

Symptoms of childhood TB are nonspecific, and up to 50% of children may be asymptomatic in the early stage [51]. The added burden of malnutrition and HIV further confound the diagnosis of childhood TB. To improve consistency among authors, experts have recently proposed clinical case definition categories (confirmed, possible, probable, unlikely, or not TB) for intrathoracic disease in symptomatic children [52].

Immunological tests

Immunological tests demonstrating T-cell reactivity to MTB derivatives are fundamental to LTBI diagnosis [53]. TST is still considered the gold standard compared with IFN-γ release assays (IGRAs). Neither IGRA nor TST are designed to diagnose TB, as they do not distinguish between LTBI and TB disease [35, 54].

BCG vaccination may interfere with TST results in low-TB prevalence communities, while in high-TB burden populations its impact on positivity is limited to young children <4 years of age [35, 49]. Reduced levels of TST positivity, as low as 20%, have been reported in children with TB disease [18]. Furthermore, fewer extrapulmonary TB patients than pulmonary TB patients had positive TST results [5]. However, a cohort study showed a predictive interest for TST value in children aged 6–10 years, as a strong tuberculin reaction predicted TB in adolescents after an initial quiescent period [22].

In LTBI, good agreement between IGRA tests was reported, while agreement between TST and IGRA was moderate, particularly in older children [8, 54, 55]. Within contacts, the proportion of children with positive IGRA increased with adult infectiveness [56]. IGRA responses were similar regardless of contacts BCG status [56]. In the absence of a gold standard for LTBI, the ''true'' sensitivity of these tests cannot be assessed directly and the predominately sensitivity driven negative predictive value for progression in the first years, following recent infection, is very high and nearly identical for both IGRAs [57]. According to a meta-analysis, during active TB, IGRA sensitivity range in children was 60–100% and specificity was 85% [58]. IGRAs could be more useful in TB disease when using cells from the site of disease, for example bronchoalveolar lavage or cerebrospinal fluid (CSF) [53, 59].

Rates of indeterminate IGRA results vary from 0 to 35%, and are particularly high in very young children and immunocompromised populations [53–56, 59]. HIV infection decreased positive IGRA rate, even in the presence of a well-preserved CD4 count [60]. In refugee children, IGRA failure rates reached 15%, largely because of insufficient mononuclear leukocyte yields [61]. Consequently, recommended cut-off points were questioned in young children [37].

Recent studies have identified markers measured in Quantiferon (Cellestis Limited, Carnegie, Australia) supernatants, potentially able to discriminate between LTBI and TB disease, such as IFN-α2, IL-1 receptor-α, sCD40L, vascular endothelial growth factor and IP-10, that are even expressed in cases of HIV infection [56, 62]. Using TST, IGRA and IP-10 together, and considering any positive test, would identify LTBI in 70% of contacts exposed to paucibacillary adult cases. These data suggest that a significant proportion of children with asymptomatic infections may be missed by a single test [56].

A gold standard for LTBI diagnosis in children is still lacking. In low- and middle-income countries, IGRA use is not recommended in children irrespective of HIV status [63]. In high-income countries, recommendations vary as to whether IGRA should replace TST or be used as a confirmatory tool.

Bacteriological confirmation

The absence of an operational gold standard to diagnose childhood TB has encouraged the use of latent class analysis [64]. However, the resulting sensitivity and specificity are highly dependent on the previously assumed relationships and clinical scoring is no longer recommended [63]. Indeed, bacteriological confirmation is mandatory whenever possible [63]. Smear microscopy performs poorly in both sputum and gastric liquid aspirates (GLA). Among TB suspects, the culture yield for MTB per patient is <15% [5, 65]. As TB disease is

TABLE 2 New sampling methods and laboratory techniques

Technique	Reference	Comment	Diagnostic yield
Sampling			
Expectorated sputum	[5]	Older children	<15%
Induced sputum	[65, 66]	No age limitation if completed by suction at the end of the induction Obtaining two samples is advised	Increases diagnostic yield by 20%
NPA	[67]	Young children No equipment required	30% if Xpert used
GLA		Three samples are advised, or carry out in association with induced sputum	38%
FNAB	[63]	Peripheral lymph node	High diagnostic yield
TBNA	[68]	Mediastinal lymph node through fibroscopy, trained endoscopist	50%
String test	[69]	Children aged >3 years	
Bacteriological laboratory			
Smear	[5]	Low sensitivity (15%)	
MGIT (gold standard)		Shortened time *versus* Löwenstein–Jensen	LED fluorescence facilitates interpretation
MODS		Less costly than MGIT [72, 73]	Less sensitive and specific than MGIT
Xpert MTB/RIF	[70, 71]	Twice as sensitive as a smear Allows concomitant rifampicin resistance detection Immediate results	Lower sensitivity than culture (57%) Shorter time to diagnosis useful in extrapulmonary TB

NPA: nasopharyngeal aspirates; GLA: gastric liquid aspirates; FNAB: fine-needle aspiration biopsy; TBNA: transbronchial needle aspiration; MGIT: mycobacterial growth indicator tube; MODS: microscopic observation drug susceptibility; TB: tuberculosis.

confirmed bacteriologically much more frequently in prospective studies than in observational data, new sampling and laboratory techniques should dramatically improve the diagnosis (table 2).

Sample collection

Alternative methods of sample collection include nasopharyngeal aspiration (NPA), hypertonic saline–induced sputum collection , which is reported to be more sensitive than GLA [24, 65], string test and lymph node fine-needle aspiration biopsy (FNAB). Induced sputum was reported to be successful in the majority of the patients, irrespective of age, without any major adverse event increasing the diagnostic yield by >20% [65, 66]. Although less frequently positive than induced sputum, NPA is easy to perform [67]. String test has been proposed as an adjunctive sample tool, and is well tolerated by patients as young as 4 years of age [69]. Data are still lacking on its efficiency in TB diagnosis. FNAB of enlarged peripheral lymph glands has been demonstrated to give a high bacteriological yield [63, 69]. In high-risk populations, FNAB using a combination of cytomorphology, autofluorescence, and Ziehl–Nielsen staining provides a rapid and definitive diagnosis of mycobacterial infection in 60% of the children sampled [69].

New bacteriological techniques

The microscopic observation drug susceptibility (MODS) assay is an inexpensive liquid culture-based method. In children with TB, MODS demonstrated a higher sensitivity than smear. A MODS assay required a shorter median time to detect MBT growth than usual liquid culture, but was less sensitive and specific [72, 73].

The Xpert MTB/RIF assay (Cepheid Inc., Sunnyvale, CA, USA) is the most popular molecular diagnosis test. Xpert MTB/RIF represents a paradigm shift in the diagnosis of TB and drug-resistant TB by simultaneously detecting MTB and rifampicin resistance-conferring mutations in a closed system suitable for use outside conventional laboratory settings in less than 2 h, directly from sputum samples [74]. In children with pulmonary TB, Xpert MTB/RIF consistently outperformed sputum and GLA smear tests, diagnosing 47% of smear-negative TB patients [6, 51, 70, 75]. For smear-negative cases, the incremental increase in sensitivity from testing a second specimen was 25% for Xpert MTB/RIF, compared with 13–17% for culture [67]. Using Xpert MTB/RIF on two induced sputum specimens detected twice as many cases (75.9%) compared with sputum smear (38%) resulting in an overall Xpert MTB/RIF specificity of 98.8%. Xpert MTB/RIF

diagnosed pulmonary TB in 51.2% of older children in a high HIV prevalence setting [74]. However, several specimens produced an indeterminate Xpert MTB/RIF result and had to be repeated [70].

Compared with culture, the pooled sensitivity estimate of Xpert MTB/RIF on sputum and GLA was 96% in smear-positive and 55% in smear-negative children, with a pooled specificity of ⩾98% for all groups [70, 71, 74, 76]. Xpert MTB/RIF showed a trend towards reduced sensitivity among children aged 0–4 years or with HIV infection [6, 76]. High sensitivity (87%) of Xpert MTB/RIF was reported in samples from children with extrapulmonary TB [76, 77]. Specificity values varied from 81% to 99% [76, 77]. Sensitivity was increased in pleural fluid (100%) and peripheral lymph nodes (86%) compared with CSF (75%) [77].

Among smear-positive, culture-negative cases, some were Xpert MTB/RIF positive and might represent false negatives [70], questioning whether culture can be considered the "gold standard" in children. Indeed, an improved diagnostic technique should have low specificity relative to culture, identifying disease missed by culture [78].

The most recent WHO recommendations [63] are that Xpert MTB/RIF should be used rather than conventional microscopy and culture as the initial diagnostic test in children suspected of having multidrug-resistant (MDR)-TB or HIV-associated TB, or in cases of TB meningitis testing CSF [63, 74].

A genome-wide RNA expression study undertaken in a large population of children with suspected TB identified a 51-transcript signature distinguishing TB from other diseases with a sensitivity of 82% and a specificity of 83% against culture [71]. The risk score also distinguished TB disease from LTBI, with a sensitivity of 94% and a specificity of 100% [71]. A 10-gene signature correctly classified 78% of TB cases in Amerindian children [79]. However, the translation of transcriptional signatures into diagnostic tools is still challenging.

Urinary detection of lipoarabinomannan is considered useful in HIV-positive adults, but this test showed insufficient sensitivity and specificity in children [80]. The electronic nose, using either urine and/or breath volatile organic compound biomarkers, displayed low sensitivity and specificity [81].

Multiple samples from different sites and expanding Xpert MTB/RIF use could dramatically improve confirmation rates in childhood TB. However, simple and sensitive tests, which are easy to perform in infants and young children, are still required.

Drug-resistant TB

Among children living with drug-resistant patients, an overall high prevalence of TB was observed (7.5%), regardless of the age of the child [82]. In places where the rates of drug-resistant TB have been monitored, the rates among children were similar or slightly higher than those among adults [2, 20]. In Namibia, South Africa, Germany, the UK and the USA, MDR-TB was positively associated with being aged <15 years [20]. An Egyptian study detected an overall drug resistance of 24% in children with TB, with a MDR-TB prevalence of 2.7%. Alarmingly, resistance to second-line drugs was 2.7% for amikacin and 1.4% for ciprofloxacin [83]. In Thailand, 5.7% of specimens from children were MDR-TB in 2012 revealing a drastic increase in a few years [51]. Furthermore, in a recent Indian survey, half of the children with drug sensitivity tests (DSTs) harboured drug-resistant strains, of which 50% were MDR-TB [18]. An epidemic of extensively drug-resistant (XDR)-TB was discovered in an Italian school *via* contact tracing of a 12-year-old patient (Italian native) with pulmonary XDR-TB. Five cases were diagnosed with TB and 19 with LTBI (12 out of 19 were in children). The index case was probably a schoolmate originating from Eastern Europe [84].

Diagnosing drug resistance requires culture and DST. Consequently, initiation of appropriate treatment has been delayed in children for between 2 and 9 months [85]. Xpert MTB/RIF has improved the diagnosis of drug resistance giving immediate results. It was 86–100% sensitive and 97% specific for the detection of rifampicin resistance in children compared with culture. However, when possible, confirmation with classical DST is still required [20, 51, 70, 76]. More work should be done to improve Xpert MTB/RIF sensitivity in paucibacillary patients [20, 51].

While adults represented the contamination source in most cases, in resource-limited settings with a high-burden of TB, the results of DST from adult index cases were not systematically used to investigate drug resistance in children [20]. Moreover, the index case was not found in 17–45% of cases [86, 87], highlighting the importance of improved reverse contact tracing. However, in TB high-burden countries, children may be exposed to several TB cases, with different susceptibility patterns [88].

Few children had a previous diagnosis of TB, suggesting that most children acquired an already resistant strain from their index case [87, 88]. However, in the most recent South African survey, 59% of children who were infected with HIV had previously received >1 month of anti-TB treatment, compared with 15% for children who were not HIV infected. Drug resistance occurred in a significantly higher proportion of children who had received previous treatment for TB than in untreated patients [88]. In Thailand, prior treatment for TB disease was associated with drug resistance, while this was not the case with anterior

treatment for LTBI [51]. Children living in settings where the prevalence of HIV is high or where resistance to isoniazid is high should be suspected of MDR-TB [89].

Imaging

Patients <3–4 years of age have the highest lymph node involvement, but the least parenchymal lesions compared with older children [52, 90]. The pivotal role of chest radiography in TB diagnosis is, however, impaired in young children, without any improvement when adding a lateral view [91]. In a South African study of TB suspects, although 75% of culture-positive children were symptomatic, only 28% demonstrated radiological evidence suggestive of TB [92].

While computed tomography (CT) is more sensitive than chest radiography [9, 91, 93], attitudes towards children with lesions observed only on CT scans are contrasting. Some authors consider that these abnormalities should be ignored and the case classified as LTBI [19]. During an outbreak of TB in a nursery, based on CT scans, 96% of the TST-positive children were diagnosed with TB disease [9]. In 60–85% of children with normal chest radiography, the CT scan showed adenopathies or a pathological infiltrate [9, 90]. In infants, chest CT scans revealed extensive parenchymal lesions and hilar/mediastinal lymph node enlargement in all cases [94].

Airway complications are frequently missed by chest radiography. Compared with endoscopy, CT scan sensitivity for prediction of severe bronchial involvement was 100%, but specificity was only 72% [95].

Bronchoscopy

Early detection and effective treatment of endobronchial TB is essential in order to decrease secondary bronchial stenosis and bronchiectasis [95–97]. Fibroscopy showed airway anomalies in half of the children with lymphadenopathy on chest radiography. Severe disease with gross extrinsic compression or obstructive endoluminal mass was found in 18.9% of the cases. However, several patients with severe disease were symptom free [95]. Mediastinal lymph nodes may be sampled safely using transbronchial needle aspiration (TBNA) through flexible bronchoscopy [68]. A prospective study in 28 children with large subcarinal lymphadenopathy reported that TBNA provided a definitive diagnosis of mycobacterial infection in 50% of patients [68].

CT scan and bronchoscopy are useful in infants and young children whenever usual tools are inconclusive. They are of particular interest when bronchial complications are suspected.

HIV co-infection

In 2009, an estimated 2.5 million children <15 years of age were infected with HIV, with the majority living in sub-Saharan Africa [98]. HIV prevalence among children with TB, in countries with moderate-to-high prevalence, ranges from 10% to 60% [99]. In the UK and USA, the incidence of TB in HIV-infected children was less than 1 per 100 child-years contrasting dramatically with the value of 23 per 100 child-years in South African townships [99]. Furthermore, according to South African surveys, HIV co-infection increased in 10 years from 7% to 26% of the tested children with TB [88]. Advanced immunosuppression and receiving antiretroviral therapy (ART) for <6 months drastically increase the risk of TB [98]. In the absence of ART, more than 20% of HIV-infected children living in high-burden areas would develop TB disease, leading to a three- to six-fold higher mortality [98, 100].

The diagnosis of TB disease in HIV-positive children is particularly difficult because of HIV-related comorbidities and chronic lung disease [24]. HIV-positive children must, therefore, be screened routinely for TB and HIV testing should be offered to all TB suspects [63]. Although HIV-positive children are more prone to develop disseminated and rapidly progressive TB, the clinical presentation is usually similar to that seen in HIV-uninfected children, but with more severe features such as concomitant extrapulmonary TB [24, 101]. Cavitation is infrequent [101]. Sophisticated diagnostic techniques are more frequently required in HIV patients.

Immune reconstitution syndrome (IRIS) is observed after the initiation of ART in severely immunocompromised patients. It induces transient worsening of TB manifestations such as fever, lymphadenopathy, pleural effusions, respiratory distress and exacerbation of cerebral tuberculomas [24]. In Thailand, IRIS was documented within 4 weeks of the initiation of ART in 19% of children with low CD4 cell percentages [24]. However, extensive delays in starting ART should be avoided [99, 100]. Current recommendations for co-infected children are that ART should be initiated 2–8 weeks after starting TB treatment [63, 100, 101]. Early ART initiation is the most important intervention for reducing overall mortality and TB risk among HIV-infected infants [2, 102]. Among children considered free of TB at ART enrolment, TB incidence was 6.28 per 100 child-years during days 0–90 of ART, demonstrating the importance of initial TB screening [23]. A better integration of HIV and TB services with general child health clinics is required [103].

Treatment

Despite a recent WHO update on childhood TB treatment regimens (table 3), there is a lack of child-friendly formulations matching these new recommendations [1, 63].

The recommended isoniazid dose of 5 mg·kg^{-1} body weight in childhood TB leads to lower serum concentrations than those recommended for adults [104]. Pharmacokinetics data confirmed that children aged <2 years achieve target concentrations using the revised WHO dosage recommendations [104, 105]. However, retrospectively, reported clinical responses to treatment and outcomes were similar with current recommended dosages and with lower dosages [106]. Intermittent treatment is less effective in achieving cure in children than daily doses, even if it is better tolerated in some cases [107, 108]. Addition of a fourth drug such as ethambutol is necessary in complicated pulmonary TB or meningeal involvement [36]. Safety of ethambutol in children is confirmed, but recommended doses are probably too low for young children [24, 109]. For infants <6 months of age with widespread dissemination, ethionamide use was reported in place of ethambutol considering its superior penetration into the central nervous system [94].

Children aged <1 year and those with severe TB or extrapulmonary TB were more likely to have poor treatment outcomes [5]. Paradoxical unexplained deteriorations occurred in 14% of non-HIV paediatric patients within a median time of 80 days. Many patients improved with corticosteroids, suggesting an exacerbated immunological response [110].

A poorer response to treatment among HIV-infected children leads to prolonging TB treatment to 9 months, although there is no evidence supporting this practice [24, 101]. In addition, the effect of HIV co-infection on the pharmacokinetics of anti-TB drugs in children requires further investigation [104].

In high-prevalence low-resource settings, the concept of relevant disease is used to decide which children will be treated, and leads to consideration of mild TB cases as LTBI [24]. However, there is no evidence of the accuracy of this concept, which can be summarised as choosing between treating patients or limiting disease diffusion within the community [1, 24]. In most settings, children with TB continue to be given low priority by national TB control programmes because they are less likely to transmit disease [1].

Additional medications

Steroid therapy is usually indicated in cases of severe bronchial obstruction [111]. Combining 4 weeks of steroids and possibly endoscopic resection demonstrated good results and dramatically reduced the need for surgery [95, 96]. In severe pulmonary TB, additional antibiotics may be required for bacterial co-infections [94].

Antiretroviral therapy

The optimal antiretroviral regimen for children receiving TB treatment has not been established, as rifampicin induces significant reductions in serum levels of several ART drugs. Rifabutin has fewer drug interactions but is associated with ocular toxicity [63]. In older children receiving rifampicin, two nucleoside reverse transcriptase inhibitors should be associated with Efavirenz; additional studies are required for young children [112]. Treatment should not be interrupted during IRIS except in cases of central nervous system TB, where IRIS can have devastating consequences [2]. Severe IRIS may require a course of glucocorticoids [2].

New recommended regimens are widely used for childhood TB. However, specially designed randomised controlled trials determining the best drug associations and required treatment duration are still required in children.

TABLE 3 Recommended daily dosages of anti-tuberculous drugs

Drug	Mean dose	Range	Maximal dose
Isoniazid (H)[#]	10 mg·kg^{-1}	7–15 mg·kg^{-1}	300 mg·day^{-1}
Rifampicin (R)	15 mg·kg^{-1}	10–20 mg·kg^{-1}	600 mg·day^{-1}
Pyrazinamide (Z)	35 mg·kg^{-1}	30–40 mg·kg^{-1}	
Ethambutol (E)	20 mg·kg^{-1}	15–25 mg·kg^{-1}	
Amikacin		15–22.5 mg·kg^{-1}	1000 mg
Ofloxacin		15–20 mg·kg^{-1} twice daily	800 mg
Ethionamide		15–20 mg·kg^{-1} twice daily	1000 mg
Cycloserine		10–20 mg·kg^{-1} once/twice daily	1000 mg
Para-aminosalicylic acid		150 mg·kg^{-1} 2–3 times daily	12 000 mg

[#]: the higher end of the range for isoniazid dose applies to younger children, as the children grow older the lower end of the dosing range becomes more appropriate. Data from [63].

Second-line drugs for MDR-TB

Despite advanced disease at presentation and a high prevalence of HIV co-infection, children with MDR-TB can be treated successfully, using individualised treatment under routine conditions [86]. A meta-analysis reported excellent outcomes in children, with a cure rate of 82%, mortality of 6% and adverse events in 39% of cases [85]. Mortality was associated with malnutrition, HIV and extrapulmonary TB [86]. Lack of weight gain was a warning sign for treatment failure [85, 105].

The South African protocol included, in the majority of cases, high-dose isoniazid as isolates with an inhA promoter region mutation usually have a low minimum inhibitory concentration [105]. Benefits of fluoroquinolones outweighed the risks and they should be use systematically [63, 86]. Ethionamide, para-aminosalycilic acid and cycloserine were used successfully, but tolerance was controversial [36, 86, 87, 113]. Success was higher when treatment included injectable drugs, although these induced hearing deficit [36]. Linezolid-containing regimens can be effective even after failing second-line treatment, but adverse events should be monitored [114].

In the absence of a sufficient number of medicines to which a strain is sensitive *in vivo*, life-saving treatment may rely on the use of new medicines such as bedaquiline or delamanid, despite the absence of data in children. The European Respiratory Society/WHO TB Consilium was implemented to face drug-resistant TB in Europe. It supports clinicians through a platform that rapidly provides four expert opinions on how best to manage a complex case [84]. It recently recommended inclusion of one of either bedaquiline or delamanid in a regimen that included meropenem and clofazimine for a 12-year-old patient with XDR-TB. Delamanid was procured in a compassionate way *via* the manufacturer. Initial clinical, laboratory and radiological improvements were observed [84].

Reported results of MDR-TB treatment are encouraging, but well conducted clinical trials are urgently needed for MDR-TB in children, to improve treatment safety and efficiency.

Prevention

BCG

BCG remains the only available vaccine for TB worldwide [35]. The global BCG efcacy is estimated to be ~50%, ranging from a zero effect to 80% [115, 116]. In addition, BCG vaccination at birth halved neonatal mortality from non-TB infections [117]. At US $2–3 per dose, BCG vaccination costs US $206 per year of healthy life gained [118].

As BCG is a live vaccine, the absence of a competent immune response can lead to disseminated BCG disease in 1% of HIV-infected infants with an all-cause mortality rate of 75–86%. IRIS frequency after vaccination is estimated to be ~15% in HIV-infected children [119]. Consequently, the WHO Global Advisory Committee on Vaccine Safety recommends that BGC should not be administered in HIV-infected patients [1]. However, a case–control study reported that childhood BCG that caused a scar decreased TB risk in adulthood by 70%, irrespective of HIV status [6, 115]. In case of disseminated BCG disease, the appropriate combination of anti-TB drugs should be used taking into account inherent resistance to pyrazinamide and variable BCG resistance to isoniazid [119].

BCG discontinuation demonstrated adverse effects in low incidence countries, for example France or Sweden. Universal BCG vaccination replacement by a targeted vaccination programme resulted in very low BCG vaccination coverage, leading to a 15-fold increase in TB incidence in children born to parents of foreign origin [120, 121].

The dynamic interaction of age and immunity, as well as its influence on pathogen evolution, needs to be considered in the development of future vaccination strategies. The best time for vaccination should be determined as maximal efficacy is not obtained before the age of 2 years, while BCG realised at birth prevents severe diseases in infants [21]. The modern vaccine should also protect against milder diseases [92]. The development pipeline now includes 12 new vaccines which can either boost the initial effects of BCG or replace BCG [122]. However, no new vaccine has shown effectiveness in late phase trials [122].

Isoniazid preventive therapy

While TB control is aimed at reducing the incidence of TB by early diagnosis and treatment of infectious cases of TB, TB elimination requires focus on sterilising the pool of latently infected individuals, from whom future TB cases would be generated [57].

Isoniazid prophylaxis reduces the risk of developing TB by 59% among children aged ⩽15 years, excluding children in whom primary prophylaxis was initiated before 4 months of age [4, 35, 123]. It was more effective among children aged 5–15 years than among children aged <5 years [123]. Screening for disease

and treatment with isoniazid preventive therapy (IPT), without testing for MTB infection, is considered the most cost-effective strategy in 0–2-year-old children [124].

A marked protective effect was demonstrated against TB disease and mortality among HIV-infected children [125], so IPT is recommended for any HIV-positive child with TB exposure, irrespective of the child's age or TST result, once active TB has been excluded [24]. However, there is, as yet, not enough data to guide the duration of prophylaxis, or to support its use in children on ART and in those living in low TB prevalence areas, without TB contact [126, 127]. The protection offered by 6 months IPT appears to be short-lasting among HIV-infected persons in high-burden TB areas [128]. In the same way, IPT was safe but ineffective as pre-exposure prophylaxis against TB [2, 129].

A low peak serum concentration of isoniazid was found among young children given isoniazid daily at 4–6 mg·kg^{-1}, and the recommended dosage is 10 mg·kg^{-1} [13]. However, a daily dosage of 5 mg·kg^{-1} among young children was used in virtually all clinical trials that investigated IPT efficacy, questioning the necessity of using a higher dosage [128]. Providing IPT to young children poses a small risk of isoniazid monoresistant TB while in adolescents IPT poses a considerably higher risk [24, 130].

Field effectiveness may be substantially lower as a result of nonadherence that approximates 76% in South Africa [63, 123, 128]. A short-course regimen with isoniazid and rifampicin for 3 months was superior to a 9 month course of isoniazid monotherapy regarding compliance and chest radiography evolution, and showed a significant decrease in childhood TB that persisted to 12 years of follow-up [109, 131]. Data are limited for rifampicin and pyrazinamide combination therapy and for economic assessment of any regimens in children [132]. In children aged >12 years, high dose isoniazid and rifapentine combination therapy once a week for 3 months demonstrated high completion rates despite frequent adverse events [109, 133].

IPT is under prescribed and monitored. Less than 20% of the European countries collect information on LTBI treatment outcomes [134]. Among South African children hospitalised for TB, IPT missed opportunities occurred in 64% [123].

Pragmatic solutions are urgently required. Parents are often reluctant to provide preventive treatment for an otherwise well child, and are further discouraged by the long duration of preventive therapy [2].

There is evidence to support 6 months of rifampicin for contacts of isoniazid-resistant disease and it is recommended for this category in the UK [109]. MDR-TB prophylaxis is much more controversial. The high failure rate of isoniazid or isoniazid and rifampicin chemoprophylaxis and first-line therapy in children with known household exposure to MDR-TB enhances the urgent need for the evaluation of appropriate chemoprophylactic regimens for child contacts of patients with MDR-TB [88]. The WHO recommends that symptomatic children who are TST positive with a MDR-TB contact, with normal chest radiography and negative bacteriological results, should be treated with a broad-spectrum antibiotic inactive on MTB and closely monitored. If the clinical condition gradually deteriorates, empirical treatment of MDR-TB should be established [89].

A completely different approach would be to prevent the reactivation of LTBI by post-exposure vaccination, which is one of the targets of the ongoing research into development of new TB vaccines [57].

Conclusion

Towards zero death, the WHO roadmap fixes as long-term objectives for 2025 the possibility of prediction of disease progression in infected children, and implementation of new efficient vaccines against infection and disease. The roadmap insists on the necessity of shorter child-friendly treatment regimens, which have been accurately designed and tested. As an immediate point of action it underlines the need to focus on TB and HIV in pregnant females and young mothers as the best way to protect the child [3]. However, to achieve the goal of TB elimination by 2050, it will be necessary to combine the transmission-blocking approach with well-resourced LTBI treatment strategies, accelerating towards zero infections, zero cases and zero deaths [57, 135].

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