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Pediatric Tuberculosis: Global Overview and Challenges

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Tuberculosis (TB) is among the top 10 causes of death among children worldwide; however, children with TB are given low priority in most national health programs and are neglected in this epidemic. Recent technological advancements in diagnosis of TB in adults have not been validated in children. Similarly, trials of new drugs and development of pediatric formulations of standard first- and second-line drugs are lagging behind. Among human immunodeficiency virus (HIV)-coinfected children, the optimal timing for highly active antiretroviral therapy initiation and drug combinations that have minimal interactions with anti-TB drugs need further study. Although bacille Calmette-Guérin vaccine, the only vaccine available for TB, protects against disseminated and severe forms of the disease in young children, its safety in the HIV-infected population has been questioned. Multicentric trials are urgently required to help develop improved diagnostic strategies and formulate shorter, more effective, safe, and evidence-based regimens for treatment and prevention of drug-susceptible and drug-resistant TB.

Worldwide, the burden of tuberculosis (TB) has been adversely influenced by the human immunodeficiency virus (HIV) epidemic and by social and economic factors that affect health care delivery. TB in children is a direct consequence of adult TB and is a good marker of current transmission in the community. Although advances have been made in diagnostics and new drugs for treatment of TB in adults, development in children has lagged behind. This review examines the current status of diagnosis, prevention, and treatment of TB in children and highlights knowledge gaps and research priorities for each of these topics.

EPIDEMIOLOGY AND BURDEN OF DISEASE

Of the ~1 million estimated cases of TB in children worldwide, 75% occur in the 22 high-burden countries [1]. In low-burden countries, childhood TB constitutes

~5% of the TB caseload, compared with 20%–40% in high-burden countries [2, 3]. Regional data from the World Health Organization (WHO) in 2007 showed that smear-positive TB in children aged <14 years accounted for 0.6%–3.6% of reported cases [1]. However, because ~95% of cases in children <12 years of age are smear negative, these data underestimate the true burden of TB [4]. Furthermore, in countries with a high prevalence of HIV infection, there has been a marked increase in the incidence and a decrease in the peak age prevalence of infectious TB; thus, most cases now occur in young adults, who are often parents of young children [1]. This finding suggests that children in developing countries will emerge as a group at high risk; in fact, in 2007, the majority of children with smear-positive TB who were <15 years of age were in Africa and Southeast Asia. Figure 1 shows the trend in the diagnosis of smear-positive pulmonary TB (data for all types of TB not available by age) among children aged <15 years by WHO region over the past decade, with increases in these 2 regions. In industrialized countries, most childhood TB cases are detected through contact tracing and have good outcomes. This is in contrast to the case in low- and middle-income countries, where childhood TB is closely associated with poverty, crowd-

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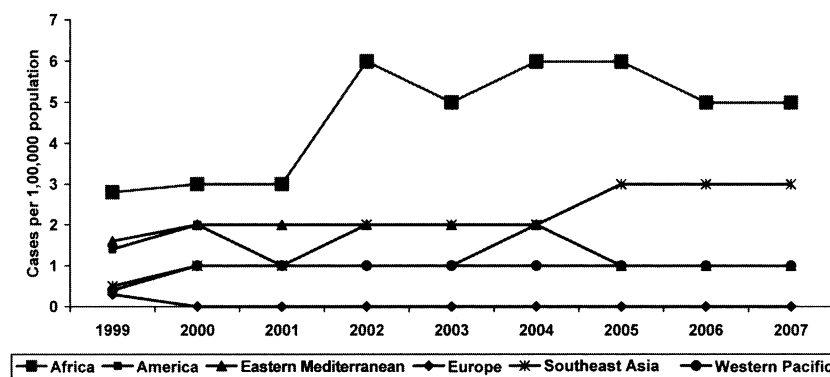


Figure 1. Trends in notification rate of new smear-positive tuberculosis cases among children aged 0–14 years (per 100,000 population). Source: WHO reports 2001–2009 [5].

ing, and malnutrition, with consequently higher death and lower treatment success rates [4].

Another unique aspect of TB in children is the imperceptible and often rapid progression from infection with *Mycobacterium tuberculosis* to disease. The risk of developing disease after infection is determined by various factors, including age at exposure, nutritional and immune status, genetic factors, virulence of the organism, and magnitude of initial infection. In the natural history of childhood intrathoracic TB, primary infection before 2 years of age frequently progresses to disease within the first 12 months [6]. Young age and HIV infection are the most important risk factors for severe or disseminated disease; the risk of disease progression decreases during childhood, is least at 5–10 years of age, and increases again during adolescence [4, 6]. Pulmonary parenchymal disease and intrathoracic adenopathy are the most common clinical manifestations of pediatric TB, accounting for 60%–80% of all cases [7]. Among extrapulmonary manifestations, lymphadenopathy is the most common (67%), followed by central nervous system involvement (13%) and pleural (6%), miliary and/or disseminated (5%), and skeletal (4%) TB [8]. Disseminated (miliary) disease and TB meningitis are usually found in very young children (age, <3 years) and/or HIV-infected children [9]. TB is among the 10 major causes of mortality among children, with a global estimate of 130,000 deaths per year [1]. Mortality has a strong correlation with socioeconomic status, underlying nutritional status and immunosuppression [10, 11]. 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 [10]. More research is required to identify better strategies for case detection and contact tracing, especially in high-burden settings, and to study the role of genetic and nutritional factors that protect children from TB infection and disease.

DIAGNOSIS

A major challenge of childhood TB is establishing an accurate diagnosis. Less than 15% of cases are sputum acid-fast bacilli smear positive, and mycobacterial culture yields are 30%–40% [12, 13]. In the absence of bacteriological confirmation, the diagnosis of childhood TB in countries where TB is not endemic is based on a triad of (1) close contact with an infectious index patient, (2) a positive tuberculin skin test (TST) result, and (3) presence of suggestive abnormalities on a chest radiograph. These criteria, however, have limited application in countries where TB is endemic, because case detection and contact tracing activities are not routine in national TB programs, transmission is not restricted to the household, and most individuals acquire infection and become TST positive during childhood and adolescence [14, 15]. Although various approaches using symptom-based diagnosis hold promise for immunocompetent children, they warrant further validation to improve specificity [15, 16]. Symptom screening also plays a role in identifying contacts eligible for preventive therapy, although its discriminatory power may be compromised in very young children or among HIV-infected persons. A practical approach is to treat children with suggestive symptoms or signs and chest radiograph abnormalities with a course of broad-spectrum (nonfluoroquinolone) antibiotics and to strongly consider the diagnosis of TB in those with minimal or no improvement. Fine needle aspiration of enlarged superficial lymph nodes and staining the smears for acid-fast bacilli are often helpful even for children who present with predominantly respiratory symptoms. Chest radiograph findings may be normal for a significant proportion of children with confirmed pulmonary TB; moreover, high intra- and interobserver variability and nonavailability limit the use of chest radiographs in resource-poor settings [17].

Collecting an adequate sample for microbiological diagnosis presents a significant challenge, particularly for small children

who cannot produce a good sputum specimen [16]. The yield of *M. tuberculosis* in culture using various specimen collection methods is shown in Table 1 [18]. The string test is a noninvasive collection method (with a higher yield than sputum induction for HIV-infected adults with smear-negative pulmonary TB) and was reported to be well tolerated by children as young as 4 years [19]. Inducing sputum after hypertonic saline nebulization has also been shown to be feasible for young children, although the most widely used procedure is still the early-morning gastric aspiration or lavage. However, all these procedures involve hospitalization, trained personnel, and attention to infection control.

Microbiological confirmation is common in adolescents and in infants and children with extensive parenchymal disease. Although culture on Lowenstein-Jensen medium is considered to be the gold standard, liquid culture systems (commercial and noncommercial) offer the possibility of more rapid and more sensitive diagnosis of active TB and drug susceptibility but are not widely available in resource-poor settings (Table 2) [16, 20]. Brittle et al [21] compared mycobacterial yields and time to detection in pediatric clinical samples with use of mycobacterial growth-indicator tubes with those with use of solid Lowenstein-Jensen slants and found that the yield was substantially higher with use of mycobacterial growth-indicator tubes (11% vs 1.6%). Furthermore, the mean time to detection could be reduced from 18.5 days to 12.4 days with use of a nutrient broth supplement; newer approaches, such as the colorimetric culture systems and phage-based tests are of interest, but limited data are available for children.

Although serum-based antibody assays offer advantages of easy specimen collection and rapidity, none of the currently available serologic tests are sensitive or specific enough for clinical use; tests developed using combinations of antigens from

a proteomics approach appear promising [22]. Polymerase chain reaction (PCR)-based tests have shown variable sensitivity in different studies, and a negative test result does not rule out TB. Conversely, a positive test result could result from cross-contamination of specimens that could occur unless high standards of laboratory biosafety and quality assurance are maintained. Currently, PCR is potentially most useful in species identification, rapid detection of drug (especially rifampicin [RMP]) resistance, and molecular epidemiology [15, 16]. Efforts are ongoing to develop tests based on detection of antigens, such as lipoarabinomannan in urine or serum samples, and cutaneous response to transdermal application of MBP64, but these need further validation in children. Detection of interferon- γ production by sensitized mononuclear cells (T-SPOT) or whole blood (interferon- γ release assay) on stimulation by specific *M. tuberculosis* antigens ESAT-6 and CFP-10 is an alternative to TST [23]. The interferon- γ release assays have not been shown to have major advantages over the TST in terms of sensitivity or specificity and are more expensive; the advantages are that they do not require a second patient visit, and they reduce the chances of human error in measurement [24–27]. It has been suggested that T-SPOT could help to discriminate between non-TB mycobacterial diseases (pulmonary and lymphadenitis) in adults and children in settings with a low incidence of TB. Currently, the major role of these tests is likely to be for latent TB in countries where TB is not endemic. Furthermore, they could potentially play a role in detection of TB in HIV-infected or malnourished children, for whom the TST performs poorly; however, this requires further research.

HIV-infected children are at risk of both atypical pulmonary presentation and extrapulmonary disease, which comprises up to 60% of TB in this population [9]. Symptom-based diagnostic

Table 1. Yield of *Mycobacterium tuberculosis* in Culture Using Various Specimen Collection Methods

Type of specimen	Yield of <i>M. tuberculosis</i> in culture, %	Remarks
Gastric lavage	40–92	Difficult, invasive procedure; increased yield in infants and patients with extensive disease; 3 consecutive specimens required after overnight fasting; can be done by trained nurses
Bronchoalveolar lavage	4–43	Extremely invasive; requires tertiary care facilities; useful if performed with diagnostic bronchoscopy
Nasopharyngeal aspiration	24–30	Less invasive; appropriate for low-income countries with limited facilities
Laryngeal swab	27–63	Useful in older children who are unable to expectorate
Induced sputum	20–30	Yield comparable to gastric lavage and nasopharyngeal aspiration; requires training; can be done by nurses; useful in hospital setting; infection-control procedures needed
String test	Not determined	Patients as young as 4 years of age tolerated the procedure well; peak discomfort at the time of swallowing and mild during string retrieval; additional studies required

NOTE. Adapted from [16, 18].

Table 2. Newer Diagnostic Tests for Tuberculosis (TB)

Test	Use in diagnosis	Advantage	Disadvantage	Validation in children
Commercial broth-based culture systems (BACTEC MGIT 960 [Becton Dickinson] and BacT/ALERT 3D [bioMérieux])	Active TB drug susceptibility; species identification	Significantly more sensitive than smear microscopy; automated, standardized reading of samples; faster than solid media culture for diagnosis (7 days for sputum positive; up to 42 days for a negative result); DST 8–12 days (starting from culture)	Expensive; requires specific training of technical personnel; liquid media prone to contamination; automated machines need maintenance; BSL-2 facilities required	Sensitivity superior to solid culture
MB redox (Heipha Diagnostika)	Active TB	Simplified 96-well plate format; does not require specialized machine	Can not be used to measure DST; visualization not easy; very few reports available; relatively slow (16 days for smear-positive sample; 3 weeks for a negative result)	Not validated in children
Solid culture colorimetric systems (eg, TK Medium [Salubris])	Active TB drug susceptibility; species identification	Simple, rapid results (3 weeks); low cost; suitable for coinfecting patients and children, because any sample site can be cultured	Published evidence limited	No data for children
Phage-based tests (eg, FASTPlaque TB test, FASTPlaqueTB Response kit [Biotech Laboratories], and FIND)	Active TB, RMP resistance	Speed (2–3 days); performs poorly on clinical samples	Labor intensive; high rate of contamination; requires full laboratory infrastructure; detects RMP resistance accurately in culture isolates	No data for children
Culture-based method (noncommercial; nitrate-reduction assay; Griess method)	Drug susceptibility	Rapid results (10 days); minimal training; visual read out of results; sensitive and specific for INH and RMP results	Only DST for INH and RMP; laboratory should have capacity to perform solid culture	No data in children
MODS assay (liquid media; PATH and Tulin Diagnostica)	Active TB drug susceptibility	Faster than solid culture results (7–10 days; maximum, 14 days); DST can be set up simultaneously; inexpensive	Requires experienced and trained personnel; thus, individual laboratory quality varies; biosafety concerns; labor intensive	Limited information for children
Non-culture-based method (antigen detection; LAM urine test [Chemogen])	Active TB	Noninvasive; done on urine specimen; simple, rapid point-of-care test; may be more sensitive among HIV-coinfected patients	Requires skilled staff, electricity supply, cold chain, and specific equipment; boiling and centrifugation of urine required; low sensitivity	Not well validated for adults or children

Table 2. (Continued.)

Test	Use in diagnosis	Advantage	Disadvantage	Validation in children
Nucleic acid amplification (molecular line probe assay [INNO-LiPa Rif.TB], GenoType MTBDR and MTBDRPlus, Hain Lifescience Automated detection and MDRTB screening, Cepheid GeneXpert device and Xpert MTB cartridge [Cepheid]; simplified NAT test, TB-LAMP [Eiken Serological tests])	Active TB drug susceptibility; active TB	Can be used to confirm TB and detect INH and RMP resistance simultaneously, but only validated for use in smear-positive clinical specimens or for testing isolates grown in culture; robust; easy to use in a routine PCR laboratory; fully automated detection of mycobacteria and resistance mutations; fast, safe results available in 2 h; cartridges stable at room temperature; sample preparation simplified; rapid, all-in-one point-of-care test; rapid, simple testing format; can be performed for all age groups and different forms of TB	Expensive; lacks an internal control; sensitivity lower from sputum samples; BSL-2/3 facilities required; sophisticated equipment, reliable energy supply, and maintenance required; reagents currently require cold storage; data on cross-contamination and test performance are needed; previous version had low sensitivity; no test with specificity >90% had sensitivity >30%; lack of reproducibility across patient groups and geographic areas	No data for children; not validated for children; tested for children; none found accurate enough for routine use

NOTE. BSL, biological safety levels; DST, drug-susceptibility testing; INH, isoniazid; PCR, polymerase chain reaction; RMP, rifampicin.

approaches perform poorly, because other HIV-related conditions, such as lymphocytic interstitial pneumonitis, bronchiectasis, and respiratory infections (including viral pneumonitis), mimic the clinical and radiographic features of TB [28]. Lymphocytic interstitial pneumonitis tends to occur in children aged >2 years, presents with recurrent respiratory symptoms, and is associated with clubbing and generalized lymphadenopathy and a miliary TB-like picture on chest radiograph. Although these patients improve temporarily with antibiotic therapy, antiretroviral treatment is required for sustained benefit and to avoid development of chronic lung disease.

In the short term, there is little prospect of achieving a widely available gold standard diagnosis of TB in children either by means of culture, microscopy, PCR, or serological testing. Consequently, clinicians must rely on clinical criteria, chest radiography, and tuberculin testing, and attempts must be made to improve the predictive power of available tools [3].

TREATMENT AND MONITORING

The basic principles of treatment and recommended standard anti-TB regimens for children are similar to those for adults [29]. Treatment for most forms of pulmonary and extrapulmonary TB consists of a 6-month short-course chemotherapy regimen with 4 drugs (isoniazid [INH], RMP, ethambutol

[EMB], and pyrazinamide [PZA]) in the initial intensive phase, followed by 2 drugs (INH and RMP) in the continuation phase. For uncomplicated pulmonary disease (primary complex) and single-site lymph node disease, EMB may be omitted from the intensive phase. Current recommendations advise extension of treatment to 9–12 months for miliary, meningeal, bone and joint, or disseminated TB. Doses for children are usually extrapolated from adult pharmacokinetic studies, and recent data point to the inadequacy of currently recommended doses of RMP, INH, and EMB. Children eliminate INH faster and require a higher body weight dose (mg/kg) to achieve serum concentrations comparable to those in adults; 10 mg/kg should be recommended rather than 5 mg/kg [30]. Low serum RMP concentrations have been documented in both HIV-infected and uninfected children receiving the standard dose of 8–12 mg/kg, which suggests that use of 10–20 mg/kg of RMP would be more appropriate [31]. With a dose of 30 mg/kg of PZA daily, efficient serum levels were reached after oral administration of PZA alone or in combination with INH and RMP [32]. A review by Donald et al [33] concluded that EMB at a daily dose of 20 mg/kg (range, 15–25 mg/kg) and a dosage of 30 mg/kg given 3 times per week was safe in children of all ages; lower doses were ineffective. Correct doses of anti-TB drugs is an essential prerequisite for complete cure, and the conse-

quences of suboptimal blood levels include treatment failure and drug resistance. On the basis of these findings, WHO guidelines for treatment are likely to be revised in 2010. Pharmacokinetic studies to establish optimal doses (daily and intermittent) of first-line and newer anti-TB drugs are urgently required to provide evidence-based recommendations in children. A further issue that needs attention is making available pediatric formulations (both individual and fixed-drug combination tablets with good bioavailability); although liquid formulations are easy to administer to young children, they are bulky, more expensive, and have unacceptable toxicity in some instances (eg, INH syrup, which causes diarrhea because it is a sorbitol-based solution).

Therapeutic trials involving children have found favorable responses of >90% with most short-course regimens for treatment of TB lymphadenitis and pulmonary TB, (Table 3) [34–42]. A meta-analysis comparing daily and intermittent (mostly twice-weekly) regimens found that, although overall favorable responses were high and death, relapse, and adverse events were uncommon with all regimens used, there was a trend to a lower cure rate with the use of twice-weekly regimens [43]. The outcome of TB meningitis correlated with the stage of disease at treatment initiation, underlining the need for early detection and prompt treatment [35]. Monitoring of response to treatment is usually based on symptomatic improvement, weight gain, or regression of radiographic findings, which can often take months or years. In a long-term follow-up study involving children treated with short-course chemotherapy, ~50% had residual lesions at the end of treatment [44]. When possible, follow-up sputum examinations should be performed at the same frequency as that for adults.

The WHO strategy of using standardized treatment regimens (based on disease severity and history of treatment) and ensuring adherence with use of directly observed treatment has been accepted and implemented in most resource-poor countries. Population-based studies have shown that case-finding, classification, and treatment of children is feasible in programs using the directly observed therapy short-course strategy; outcomes were worse in young children and when adverse events occurred (Table 4) [45–50]. Other reasons for low success rates in low-income countries include poor compliance and non-completion of treatment, late presentation by patients and delay in diagnosis by health care workers, incorrect diagnosis, high early mortality in children with advanced HIV infection, malabsorption of anti-TB drugs in HIV-infected or severely malnourished children, and multidrug-resistant (MDR) TB [51]. The proportion of cases managed by the national TB program varies by country, and nonuniform management practices used in the private sector contribute to poor outcomes.

Although it is clear that concomitant treatment of HIV infection in coinfecting children reduces morbidity and mortality,

the optimal timing of initiation of highly active antiretroviral therapy (HAART) is yet to be defined, especially in the context of drug interactions [52]. Because of the induction of cytochrome p450 enzymes, RMP lowers the level of almost all protease inhibitors (except ritonavir) by >75%, of efavirenz by 17%, and of nevirapine by 35% [53]. In addition to drug interactions, other factors that impact on antiretroviral blood levels include age, nutritional status, and genetic polymorphisms in the cytochrome p450 enzymes [54]. For children aged <3 years, appropriate dosing of efavirenz has not been determined; treatment of coinfecting children in this age group is a challenge, with many physicians either delaying treatment until anti-TB treatment has been completed or using a higher dose of nevirapine. There is an urgent need for studies of efficacy and safety of different antiretroviral drug combinations in this age group.

In the growing pipeline of potential new TB drugs, there are presently several novel compounds that are in various stages of clinical development, including the fluoroquinolones, TMC207, OPC67683, and PA824 [55]. However, new drug development for treatment of children has lagged because of the difficulty of confirming active TB, concerns about pediatric-specific adverse effects, uncertainties about the appropriate time to involve children in drug development, the optimal trial designs for drug development, and complex regulatory requirements [56].

PREVENTION OF TB

Approaches for prevention of TB include prevention of infection (through immunization) or of progression from latent infection to disease (chemoprophylaxis). Bacille Calmette-Guérin (BCG) vaccine, a live attenuated vaccine derived from *Mycobacterium bovis* that was developed in the 1920s, is administered to children at birth in many countries. A large trial in southern India that included >350,000 participants aged >1 year concluded that BCG vaccine did not offer protection against the development of adult pulmonary TB [57]. However, BCG vaccine has been shown to be protective against disseminated forms of TB in young children, with a summary protective estimate of 73% (range, 67%–79%) against TB meningitis and 77% (range, 58%–87%) against miliary disease [58]. A theoretical model estimated that a universal BCG vaccine program would have a beneficial impact in settings with prevalence rates of >30 sputum smear-positive cases/100,000 population [59]. There is no evidence of any BCG-induced protective effect in HIV-infected children. On the contrary, studies have documented BCG-induced disseminated disease and adverse reactions [60, 61]. Therefore, WHO recommendations have been revised, making HIV infection a contraindication for BCG vaccination, even in settings where TB is highly endemic [62]. Strategies required for effective implementation of

Table 3. Therapeutic Clinical Trials of Tuberculosis (TB) in Children

Reference	Country (year)	Type of disease	No. of children	Regimens	Duration of treatment	Results
Varudkhar et al [34]	India (1985)	Pulmonary TB	185	2 Months of INH, RMP, and EMB (7 times per week), 4 months of INH and EMB (7 times per week); 2 months of INH, PZA, and EMB (7 times per week), 4 months of INH and EMB (7 times per week); 6 months of INH, RMP, and EMB (3 times per week)	6 Months	No treatment failures or relapse
Ramachandran et al [35]	India (1986)	TB meningitis	163	2 Months of INH, RMP, and STM (7 times per week), 4 months of INH and EMB (7 times per week) and STM (2 times per week), 6 months of INH and EMB (7 times per week); 2 months of INH, RMP, PZA, and STM (7 times per week), 10 months of INH and EMB (7 times per week); 2 months of RMP (2 times per week), INH, PZA, and STM (7 times per week), 10 months of INH and EMB (7 times per week)	12 Months	Overall favorable response (29%–36%); outcome related to stage of disease at treatment initiation
Jawahar et al [36]	India (1990)	TB lymphadenitis	168	2 Months of STM, INH, RMP, and PZA (3 times per week), 4 months of STM and INH (2 times per week)	6 Months	Favorable response (97%)
Kumar et al [37]	India (1990)	Pulmonary TB, TB lymphadenitis, disseminated TB	76	2 Months of INH, RMP, and PZA (2 times per week), 4 months of INH and RMP (2 times per week); 2 months of INH, RMP, and PZA (7 times per week), 4 months of INH and RMP (2 times per week)	6 Months	Favorable response (97% and 100%, respectively); no relapse
Tsakalidis et al [38]	Greece (1992)	Pulmonary TB, extrapulmonary TB	36	2 Months of INH, RMP, and PZA (7 times per week), 4 months of INH and RMP (7 times per week)	6 Months	No failures or relapses

Table 3. (Continued.)

Reference	Country (year)	Type of disease	No. of children	Regimens	Duration of treatment	Results
Kansoy et al [39]	Turkey (1996)	Pulmonary TB	33	0.5 Month of STM, INH, and RMP (7 times per week), 8.5 months of INH and RMP (2 times per week); 40 days of STM, INH, and RMP (7 times per week), 9 months of INH and RMP (7 times per week), 3 months of INH (7 times per week)	9 Months; 13.3 months	No treatment failure or relapse; short duration intermittent regimen adequate
Ramachandran et al [40]	India (1998)	Pulmonary TB	137	2 Months of INH, RMP, and PZA (3 times per week), 4 months of INH and RMP (2 times per week); 9 months of INH and RMP (7 times per week)	6 Months; 9 months	No treatment failures, 3 deaths, 1 relapse (9 months of INH and RMP [7 times per week])
Te Water Naude et al [41]	Africa (2000)	Pulmonary TB	213	2 Months of INH, RMP, and PZA (2 times per week), 4 months of INH and RMP (2 times per week); 6 months of INH, RMP, and PZA (5 times per week)	6 Months	Favorable response (89% and 97%, respectively); 1 relapse (6 months of INH, RMP, and PZA [5 times per week])
Al-Dossary et al [42]	United States (2002)	Pulmonary TB, Pleural TB, TB lymphadenitis	175	2 Weeks of INH, RMP, and PZA (7 times per week), 6 weeks of INH, RMP, and PZA (2 times per week), 4 months of INH and RMP (2 times per week)	6 Months	81% Treatment completion; 1 relapse

NOTE. INH, isoniazid; PZA, pyrazinamide; RMP, rifampicin; STM, streptomycin.

this policy change include high uptake of maternal HIV testing coupled with implementation of proven strategies to prevent mother-to-child HIV transmission, including maternal treatment with HAART and early virological diagnosis of HIV infection in infants, followed by treatment.

The revised recommendations present a dilemma for national programs. Although the benefits of BCG vaccine far outweigh the risk among HIV-uninfected children living in high areas with a high prevalence of TB, the risk is higher among HIV-infected infants with or without symptoms at the time of vaccination. National recommendations will need to consider a variety of factors, including the prevalence of TB in the population, the prevalence of HIV infection, the availability of HIV testing and facilities for prevention of mother-to-child transmission during pregnancy, the capacity to conduct follow-up of vaccinated children, and the availability of early infant di-

agnosis of HIV infection. Abandoning the use of BCG vaccine before newer vaccines become available may put millions of young children at risk of TB. There is an urgent need for operational research in countries to determine the best way to manage this issue programmatically.

The classic trials of treatment for latent TB infection were conducted by Ferebee and colleagues [63] in the 1960s and established that INH administered daily for 6–9 months was effective in preventing TB in adults and children with latent TB infection. Short-course regimens of INH and RMP for 3–4 months appear to be safe and superior to 9 months of INH monotherapy, mainly because of better compliance [64]. In HIV-infected children, preventive therapy has the potential to play a major public health role by reducing the incidence of TB and TB-associated mortality. A clinical trial that randomized 263 HIV-infected children to receive INH or placebo with tri-

Table 4. Population-Based Studies of Tuberculosis (TB) Treatment Outcome in Children

Reference	Country (year)	Type of study	No. of children	TB treatment outcome	Remarks
Phongsamart et al [45]	Canada (2009)	Retrospective	121	Treatment completion (87%)	Higher treatment completion rate in DOTS group
Harries et al [46]	Malawi (2002)	Retrospective	2739	Treatment completion (45%), death (17%), default (13%), unknown outcome (21%)	Treatment outcome worse in young children and in patients with smear-negative TB
Kabra et al [47]	India (2004)	Prospective	459	Treatment completion (80%); of these, 82% were cured with primary regimen, 15% required treatment extension, 3% required change of treatment	Feasible to classify and manage TB in children as in adults
Oliveira et al [48]	Brazil (2006)	Retrospective	248	Default rate (24%), frequent in first 2 months	Risk factors for default: child aged <1 year, previous default, father absent or illicit drug user
Sharma et al [49]	India (2009)	Retrospective	1098	Overall success rate (95.4% [new cases] and 82.6% [retreatment cases]), default (3%), failure (1.9%), death (1%)	DOTS is a highly efficacious treatment strategy
Oeltmann et al [50]	Botswana (2008)	Retrospective	5483	Cured or treatment completed (67%), death (10.5%)	Reported adverse drug reactions and younger age associated with death

NOTE. DOTS, directly observed therapy short-course.

methoprim-sulfamethoxazole, given daily or 3 times per week, found a marked reduction in the incidence of TB (3.8% vs 9.9%) and TB-associated mortality (8% vs 16%) in the INH group [65].

Current WHO guidelines advise that all children <5 years of age who are in close contact with a sputum smear-positive index patient should be actively traced, screened for TB, and provided preventive chemotherapy after active TB has been excluded [29]. Although this is good policy, implementation is fraught with challenges, including difficulty diagnosing latent TB in a highly BCG-vaccinated population, ruling out incipient active disease, and the lack of procedures for documentation and follow-up of contact screening and chemoprophylaxis in national programs. Because the majority of transmission in children <3 years of age occurs in the household and they are also the group at highest risk of progression to disease after primary infection, this activity should be given higher priority in national infection-control programs. Moreover, active tracing and screening of household contacts at high risk would allow children with disease to receive a diagnosis earlier, thus reducing complications.

DRUG RESISTANCE

There were an estimated 0.5 million adult cases of MDR-TB in 2007. By the end of 2008, 55 countries and territories had

reported at least 1 case of extensively drug-resistant TB [1]. Comprehensive studies on resistance to anti-TB drugs in children are lacking, because they are not included in global surveys. Surveillance of anti-TB drug resistance during 1995–2007 among children from South Africa showed a significant increase in resistance to INH or RMP from 6.9% to 15.1% and an increase in multidrug resistance from 2.3% to 6.7% [66]. Drug resistance among children has been documented in clinical trials of both pulmonary and extrapulmonary TB [67].

Management of MDR-TB is a challenge, because it requires prolonged treatment for 24 months with second-line drugs, which are more toxic and expensive than first-line drugs. According to the 2006 WHO guidelines for programmatic management of MDR-TB, an optimal regimen should include a fluoroquinolone, an injectable (capreomycin, kanamycin, or amikacin), and at least 2 of the following drugs: cycloserine, thiomides, para-amino salicylic acid, and first-line agents other than INH and RMP [68]. Experience with second-line TB drugs in children is limited; 38 children in Peru were treated with supervised, individualized regimens consisting of ≥ 5 drugs in the national program. Despite half of these children being anemic and malnourished, treatment was well tolerated and resulted in a 95% cure rate [69].

There is little published information on optimal treatment of latent TB infection in children in contact with patients with

MDR-TB. In 30-month follow-up of contacts of patients with MDR-TB, 5% of children who received appropriate chemoprophylaxis and 20% of those who did not receive prophylaxis developed disease [70]. Regimens used included INH, PZA, and ethionamide or EMB. Currently, the best approach may be to perform a complete risk assessment and clinical evaluation and to individualize therapy, while keeping these children under close observation. Multicentric trials are urgently required to determine the most effective drug combinations and optimal duration of chemoprophylaxis for contacts of patients with MDR-TB.

CONCLUSIONS

Refinement of existing tools and development and testing of new tools are urgently required to improve diagnosis and treatment of TB in children. Higher global priority and funding will be required to reduce the unnecessary and avoidable morbidity and mortality occurring currently. In addition to reducing the burden of adult TB, attention to childhood nutrition and improvement in the socioeconomic and environmental condition of communities is likely to have a significant impact on TB transmission to children.

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