SUPPLEMENT ARTICLE

Prevention, Diagnosis, and Treatment of Tuberculosis in Children and Mothers: Evidence for Action for Maternal, Neonatal, and Child Health Services

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Tuberculosis affected an estimated 8.8 million people and caused 1.4 million deaths globally in 2010, including a half-million women and at least 64 000 children. It also results in nearly 10 million cumulative orphans due to parental deaths. Moreover, it causes 6%–15% of all maternal mortality, which increases to 15%–34% if only indirect causes are considered. Increasingly, more women with tuberculosis are notified than men in settings with a high prevalence of human immunodeficiency virus (HIV), and maternal tuberculosis increases the vertical transmission of HIV. Tuberculosis prevention, diagnosis, and treatment services should be included as key interventions in the integrated management of pregnancy and child health. Tuberculosis screening using a simple clinical algorithm that relies on the absence of current cough, fever, weight loss, and night sweats should be used to identify eligible pregnant women living with HIV for isoniazid preventive therapy or for further investigation for tuberculosis disease as part of services for prevention of vertical HIV transmission. While implementing these simple, low-cost, effective interventions as part of maternal, neonatal, and child health services, the unmet basic and operational tuberculosis research needs of children, pregnant, and breastfeeding women should be addressed. National policy makers, program managers, and international stakeholders (eg, United Nations bodies, donors, and implementers) working on maternal, neonatal, and child health, especially in HIV-prevalent settings, should give due attention and include tuberculosis prevention, diagnosis, and treatment services as part of their core functions and address the public health impacts of tuberculosis in their programs and services.

Tuberculosis affected an estimated 8.8 million people and caused 1.4 million deaths globally in 2010, including a half-million women and at least 64 000 children [1]. It is intricately linked with human immunodeficiency virus (HIV), as well as noncommunicable diseases and ill-health determinants such as diabetes mellitus, smoking, alcoholism, and malnutrition [2]. The Stop TB Strategy, founded on the Directly Observed Treatment, Short-Course (DOTS) strategy, provides the framework for the global response against tuberculosis and has been implemented in virtually all countries [3]. As a result of this implementation, 46 million tuberculosis patients have been cured and 6.8 million lives saved, including those of 250 000 children and up to 1.7 million women of childbearing age [1, 4]. However, more than one-third of estimated tuberculosis cases are still not identified by existing services and systems. As a result, the global detection of estimated tuberculosis cases has been stagnating at 60%–65% between 2006 and 2010 [1]. Unfortunately, despite causing nearly 10 million cumulative orphans due to parental deaths in 2009 [1], tuberculosis prevention, diagnosis, and treatment services are still not acknowledged nor widely implemented by maternal and child healthcare stakeholders and implementers [5]. The objective of this article is to review the

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magnitude and challenges of childhood and maternal tuberculosis in high tuberculosis and HIV burden settings and to suggest policy and programmatic actions that would increase the uptake and implementation of tuberculosis care within maternal, neonatal, and child health services.

We searched the PubMed database for articles published between 1 January 2000 and 31 August 2011. Search vocabulary and key words for the ''Childhood Tuberculosis'' section included a combination of the following terms: child, children, child health services, child care, infants, pediatrics and tuberculosis, tuberculosis diagnosis, and tuberculosis therapy. Search vocabulary and key words for the ''Maternal Tuberculosis'' section included a combination of the following terms: women, female, women's health services, women's health, maternal, mother, mortality, tuberculosis, tuberculosis therapy, tuberculosis and female genital, and female infertility. We reviewed all retrieved titles and abstracts for relevance to the topic. The reference lists of retrieved studies were also reviewed to identify key articles with important and relevant information that were published before 1 January 2000. We limited the search strategy to human studies and English-language articles, and duplicates were removed.

CHILDHOOD TUBERCULOSIS

Magnitude and Burden

An accurate estimate of the global burden of tuberculosis in children is difficult mainly because of the challenges in case ascertainment, diagnosis, and weak surveillance systems in many countries with a high burden of tuberculosis [6]. Due to these reasons, children are often excluded from tuberculosis prevalence surveys [7], further hampering the collection of reliable information. It is estimated that children younger than 15 years contribute 15%–20% of the global tuberculosis burden [8]. Few countries have reported data on childhood tuberculosis, and the reported case notification rates range between 3% and 25% [9]. Table 1 shows that data reported on childhood tuberculosis cases among the 22 countries with a high burden of tuberculosis accounted for 82% of the notified cases in 2010, in which only half of the countries' reported tuberculosis cases were stratified by age and sex [1]. However, it was estimated that there were 520 000 (490 000-550 000) childhood TB cases globally (personal Communication, Stop TB Department, WHO). A national facility-based survey in Malawi in 1998 showed that childhood tuberculosis accounted for 12% of all the cases notified and for 37% of the overall smear-negative and extrapulmonary tuberculosis burden [10]. In one study from South Africa, children <13 years of age contributed to 14% of the burden, with a childhood tuberculosis incidence rate of 407 per 100 000 population per year [11]. In a cohort of children with vertically transmitted HIV infection, 36% of children were suspected to have tuberculosis on the basis of their clinical presentation, including a positive tuberculin skin test (TST), positive acid-fast bacilli (AFB) smear, and response to treatment. The median age at diagnosis of tuberculosis was 16 months, and 11% had a positive culture [12]. Abdominal tuberculosis was also the cause of 5% of acute abdomen with peritonitis and intestinal obstruction among children [13]. Perinatal tuberculosis includes tuberculosis acquired in utero, intrapartum, or during the early newborn period and is believed to be increasing [14].

The global extent of multidrug-resistant (MDR) tuberculosis and extensively drug-resistant (XDR) tuberculosis among children is unknown. A World Health Organization (WHO) drug-resistance surveillance study from 34 countries and territories showed that the frequency of MDR tuberculosis peaked for the 0–14-year age group in countries outside Central and Eastern Europe [15]. One prospective drug-resistance surveillance study conducted from 1994 to 2007 in a province in South Africa demonstrated a 3-fold increase in the MDR tuberculosis trend from 2.3% to 6.7% among children [16]. Similarly, XDR tuberculosis was reported among 4 children <10 years of age following hospitalization, which highlights the importance of proper infection control measures to prevent nosocomial tuberculosis transmission [17].

Reliable quantification of the burden of mortality from childhood tuberculosis is also lacking. A postmortem study in Zambia showed that one-fifth of children who died from respiratory illnesses had tuberculosis, of whom 60% were HIV positive [18]. Similarly, tuberculosis caused 22% of deaths among Mexican children with perinatal HIV infection who were receiving antiretroviral therapy (ART) [19]. In a hospital-based study conducted among 52 HIV-infected infants with culture-confirmed tuberculosis in South Africa, a third of them died, most of them without initiating ART [20].

The magnitude of childhood tuberculosis in a particular setting can be the reflection of the level of success of tuberculosis control activities. The DOTS strategy, based on sputum microscopy, has been the mainstay of tuberculosis control activities, including childhood tuberculosis in many countries with a high burden of tuberculosis and HIV [21]. It was argued that tuberculosis control efforts primarily relying on sputum microscopy may have had the unintentional effect of neglecting childhood tuberculosis in many national tuberculosis control programs in the early days of scaling up the DOTS strategy [22]. The Stop TB Strategy now emphasizes the equitable access to tuberculosis prevention, diagnosis, and care for all cases of tuberculosis in adults and children [3], and guidelines are available for national tuberculosis control programs [23] to effectively address childhood tuberculosis, including in children living with HIV [24].

Prevention of Tuberculosis in Children

The risk of infection by *Mycobacterium tuberculosis* in a child depends on the probability, duration, and proximity of exposure

Table 1. New Tuberculosis Cases Notified Among Women and Children for 22 High Tuberculosis Burden Countries, 2010.

Country	Total New Cases Notified, All Forms	Total New Cases Notified, All Forms, Among Children 0–14 y (%)	Total New Cases Notified, All Forms, Among Women 15–44[a] y (%)
Afghanistan	26 280	NR	NR
Bangladesh	150 903	4235 (2.8)	36 825 (24)
Brazil	70 979	2450 (3.5)	14 892 (21)
Cambodia	39 994	NR	NR
China	869 092	6710 (0.8)	150 212 (17)
Democratic Republic of the Congo	110 032	NR	NR
Ethiopia	152 030	NR	NR
India	1 227 667	NR	NR
Indonesia	296 272	28 312 (9.6)	71 914 (24)
Kenya	95 604	5721 (6)	27 044 (28)
Mozambique	42 126	NR	NR
Myanmar	127 134	NR	NR
Nigeria	81 454	NR	NR
Pakistan	255 329	24 474 (9.6)	101 294 (40)
Philippines	163 248	NR	NR
Russian Federation	102 823	831 (0.8)	20 662 (20)
South Africa	335 974	50 474 (15)	121 870 (36)
Thailand	64 512	NR	NR
Uganda	41 594	NR	NR
United Republic of Tanzania	59 668	5216 (8.7)	20 218 (34)
Vietnam	88 033	NR	NR
Zimbabwe	42 872	4371 (10.2)	14 642 (34)

Data shown are from the 22 countries with a high burden of tuberculosis, which accounted for 82% of the world's notified tuberculosis cases in 2010 [1].

Abbreviations: NR, not reported to the WHO, disaggregated by age and sex for all forms of tuberculosis (smear-positive pulmonary, smear-negative pulmonary, extrapulmonary); WHO, World Health Organization.

[a] Standard WHO reporting of notification data is done with 10-y bands (ie, 15–24, 25–34, 35–44, 45–54, 55–64, >65), so it is not possible to account for 15–49 y.

to an infectious case and on the infectiousness of the source, who is often an adult [6, 25]. The risk of disease progression following primary infection in children is highly variable depending on age and immune status [26]. The vast majority of immunocompetent children <2 years old progress to active disease within the first year of primary infection without prior significant symptoms [27]. Therefore, it is important to categorize children <3 years old and children living with HIV or other immunocompromised states of any age as high-risk groups for tuberculosis disease [28]. BCG vaccination is recommended for all infants soon after birth in tuberculosis-prevalent settings but has an average preventive efficacy of 50% against pulmonary tuberculosis [6] and contrasting reports of duration of protection ranging from <10 years [29] to 60 years [30]. Nonetheless, BCG vaccination prevents severe disseminated disease including tuberculosis meningitis and miliary tuberculosis [6]. Due to risk of disseminated disease and complications among infants with HIV [31, 32], BCG vaccination is not recommended for HIV-infected infants [33].The smooth implementation of this recommendation is impeded in many HIV-prevalent and resource-constrained settings by the lack of capacity for prompt infant HIV diagnosis. However, the benefits outweigh the risks of BCG vaccination for infants with unknown HIV status or those born to mothers with unknown HIV status in HIV-prevalent settings [33].

It is recommended that children <5 years of age with a contact history of an infectious adult tuberculosis case should receive isoniazid preventive therapy (IPT) daily for 6 months after tuberculosis disease is reliably excluded [9]. The TST is the best available way to detect tuberculosis infection in children with contact to infectious cases [9]. However, TST is not always required to initiate IPT following tuberculosis exposure in a young and immunocompromised child due to the risk of false negatives [26]. The interferon-γ release assays (IGRAs) have similar sensitivity in detecting tuberculosis infection or disease with possibly a reduced accuracy in young adults or children living with HIV [34]. Unlike TST, their performance seems not to be affected by BCG vaccination [35]. Because of the operational challenges, IGRAs should not replace TSTs in low- and middle-income countries for the screening of latent tuberculosis infection in child contacts or in outbreak investigations [35].

Children living with HIV who are >12 months of age and who do not present with poor weight gain, fever, or current cough are unlikely to have active tuberculosis disease and should receive IPT [36]. IPT was associated with a 54% reduction in all-cause mortality and a 72% reduction in the incidence of tuberculosis among children living with HIV [37]. However, no benefit of IPT was observed among HIV-infected and uninfected infants without prior exposure to tuberculosis [38]. ART use in children living with HIV leads to approximately a 70% reduction in tuberculosis incidence, which increases to 90% if used in combination with IPT [39, 40]. There is limited evidence about the usefulness of isoniazid secondary prophylaxis in children living with HIV after successful completion of tuberculosis treatment. However, because of the increased risk of exposure to reinfection and recurrence of tuberculosis, children living with HIV in high tuberculosis transmission and prevalence settings should receive IPT for an additional 6 months based on the local context [36]. In general, IPT delivery to children remains an operational challenge in both high and low HIV prevalence settings, due to a wide range of health system barriers [41], with only 16%–66% of eligible contacts receiving the drug [42–45].

Diagnosis of Tuberculosis in Children

Currently available diagnostic tools for tuberculosis rely on AFB microscopy, culture growth, and molecular DNA detection (eg, Xpert MTB/RIF test) of *M. tuberculosis* in specimens, largely in sputum. However, children, especially those <5 years old, cannot expectorate sputum [6]. Gastric aspirate, sputum induction, laryngeal swab, and nasopharyngeal aspirate are methods used to obtain samples from children, with positive AFB results ranging from 1% to 17% and culture growth ranging from 15% to 92% [46]. Multiple specimens taken over 1 day using all induction methods available (ie, gastric aspirates, nasopharyngeal aspirates, and induced sputum) had a higher yield than successive samples from any one site and reduced hospitalization and overall costs [47]. Sputum induction was safe, preferable to gastric aspirate [48], and feasible in a peripheral clinic [49] in a high HIV and tuberculosis prevalence setting. A string test in which children swallow a gelatin capsule containing a coiled nylon string later withdrawn and used for mycobacterial culture can also be used [50]. Fine needle aspiration of lymph nodes can also be used in children [51].

However, the wider use of these methods is challenged by operational issues and normally only available in high-tier facilities (ie, tertiary hospitals) in major cities in most resource-limited settings [22]. The recommended approach for the diagnosis of tuberculosis is shown in Table 2 and is similar in HIV-negative children and those living with HIV. Clinical diagnostic approaches using symptoms and signs [52], including scoring systems [46], have been used to facilitate the diagnosis of tuberculosis in children. However, they are not standardized, validated, nor adapted to malnourished children or children living with HIV [46, 52]. Score charts perform particularly poorly in children suspected of pulmonary tuberculosis and in children living with HIV [9].

Table 2. Recommended Approach for Diagnosis of Tuberculosis in Children[a]

Careful history including history of tuberculosis contact and symptoms consistent with tuberculosis
Clinical examination including growth assessment
Tuberculin skin testing or interferon-γ release assay
Human immunodeficiency virus testing
Bacteriological confirmation whenever possible (acid-fast bacilli microscopy and mycobacterial culture of specimens)
Investigations relevant for suspected pulmonary tuberculosis and suspected extrapulmonary tuberculosis (eg, Xpert MTB/RIF test, chest radiography, fine needle aspiration)

[a] Adapted from [9].

The approach recommended for national TB control programs in resource-constrained settings to diagnose tuberculosis in children includes careful history (including history of tuberculosis contact and symptoms consistent with tuberculosis), clinical examination (including growth assessment), TST, bacteriological confirmation whenever possible, additional investigations relevant for suspected pulmonary tuberculosis and suspected extrapulmonary tuberculosis, and HIV testing (in settings with high prevalence of HIV) [9]. The presence of ≥3 of the following should strongly suggest a diagnosis of tuberculosis: history of tuberculosis contact and chronic symptoms suggestive of tuberculosis, physical signs highly suggestive of tuberculosis, and positive TST or IGRA and chest radiographic findings suggestive of tuberculosis [9]. TST and IGRA do not discriminate between latent infection and active disease and can only partially assist in the diagnosis among children with signs and symptoms suggestive of tuberculosis, including those who are HIV-infected [24]. Proper identification of samples for bacteriological confirmation through microscopy and culture and for other molecular DNA detection methods is therefore important. Xpert MTB/RIF test, an automated real-time nucleic acid amplification assay that can detect tuberculosis and rifampicin resistance in <2 hours, performed on 2 induced-sputum samples, detected 76% of all culture-proven cases, including among children living with HIV [53].

Treatment of Tuberculosis in Children

The principles of treatment and the recommended regimens of drugs for each category of tuberculosis disease are generally similar between adults and children [54]. Children

with suspected or confirmed pulmonary tuberculosis or peripheral lymphadenitis and living in HIV-prevalent settings (≥1% adult HIV prevalence or ≥5% of HIV prevalence among tuberculosis patients) or in settings with high isoniazid resistance, or both, should be treated with a 4-drug regimen consisting of isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) for 2 months followed by isoniazid and rifampicin (HR) for 4 months. Similarly, children with extensive pulmonary disease living in low HIV prevalence or low isoniazid resistance settings should also be treated with 2 months of HRZE followed by 4 months of HR. A 3-drug regimen (without ethambutol) for 2 months followed by HR for 4 months can also be used for HIV-negative children with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence or low isoniazid resistance. The exception is tuberculosis of the central nervous system, bone, and joint for which 12 months' duration of treatment with a 4-drug regimen (HRZE) is recommended in the first 2 months, followed by HR for 10 months [23]. Twice-weekly intermittent short-course therapy is less likely to cure tuberculosis in children compared with daily therapy [55]. Although thrice-weekly dosing frequency has better outcomes than twice weekly, children living with HIV should receive daily dosing of a rifampicin-containing regimen [23]. Although tuberculosis drug metabolism, distribution, and clearance are likely to be different from adults, especially in young children, drug recommendations for children were largely based on pharmacokinetic data obtained from adult studies [56]. Similarly, based on clinical trial data obtained from adults, HIV-infected children should be provided with combined tuberculosis and HIV treatments as soon as possible [57]. The dosage of anti-tuberculosis drugs recommended for treatment and prophylaxis have recently been revised (Table 3), reflecting the level of evidence that is available [23, 58]. Drug-induced hepatotoxicity can occur in children at any age or at any dosage of isoniazid, rifampicin, or pyrazinamide, but the incidence of this adverse effect is considerably lower in children than in adults [59].

The absence of child-friendly drug formulations is a daunting challenge in many settings, as the production and provision of anti-tuberculosis drug preparations has largely focused on therapy for adults [60]. Children in many tuberculosis-prevalent and resource-constrained settings receive portions of adult-sized tablets rather than liquid formulations. It was suggested that tablet portions are well taken and tolerated by children and are more readily transported and stored than liquid preparations in resource-constrained settings [56]. However, difficulty in accurately crushing the tablets can lead to fluctuations in actual dosing of the drugs, especially among younger children. The revision in dosage of tuberculosis drugs and treatment regimen calls for the development of new fixed-dose combinations of tuberculosis drugs for children.

Table 3. Changes in the Dosing of First-line Anti-Tuberculosis Drugs for Children

Drug	Previous Daily Dosing (Range)[a]	Revised Daily Dosing (Range)[b]
Isoniazid	5 mg/kg (4–6)	10 mg/kg (10–15)[c]
Rifampicin		
0–3 mo	10 mg/kg (8–12)	No change
>3 mo	10 mg/kg (8–12)	15 mg/kg (10–20)
Pyrazinamide		
0–3 mo	25 mg (20–30)	No change
>3 mo	25 mg (20–30)	35 mg/kg (30–40)
Ethambutol	20 mg (15–25)	No change
Streptomycin[d]	15 mg (12–18)	No change

[a] Based on the 2006 World Health Organization guidelines [9].

[b] Based on the 2010 World Health Organization guidelines [23].

[c] The isoniazid dosing is recommended for both prophylaxis and treatment.

[d] Streptomycin should be avoided; its use is mainly reserved for the first 2 mo of treatment of tuberculosis meningitis.

Furthermore, it presents a challenge in the use of currently available fixed-dose combinations of tuberculosis drugs for children. However, interim dosing instructions for the use of existing fixed-dose combinations based on weight of the child are available and should be used in the meantime [61]. Nutritional supplements, especially in malnourished children, could help treatment of tuberculosis [6].

MATERNAL TUBERCULOSIS

Magnitude and Burden

Globally, more tuberculosis cases are reported in men than women [1], and several factors, including biological [62], clinical [63], epidemiological [64], and social [65], have been considered to explain the sex differential. There are conflicting reports about access to health services as the reason for the sex differential [63, 65], although more women with tuberculosis were detected by active case-finding strategies than by self-reporting in public sector facilities [62]. Increasingly, more women with tuberculosis are notified than men in high HIV prevalence settings, particularly in the southern part of Africa [1, 66, 67]. For example, the male-to-female ratio of notified tuberculosis cases for smear-positive pulmonary tuberculosis dropped from 1.4 in 2000 to 1.0 in 2010 in both Swaziland and South Africa [1], reflecting the increased burden of tuberculosis among women, primarily due to the feminization of the HIV epidemic. There is conflicting global evidence about the risk of MDR tuberculosis by sex. Although there was more risk of being affected by MDR tuberculosis among female patients in South Africa, the risk was higher among male tuberculosis patients in countries of the former Soviet Union [15].

Genital tuberculosis is an important cause of infertility in developing countries [68] and often poses a diagnostic challenge with atypical presentations such as ascites, vague abdominal distension, and misdiagnosis including with ovarian carcinoma [69]. The incidence of genital tuberculosis as a cause of overall infertility ranges between 1% and 16% and causes about 40% of the infertility due to problems with the fallopian tubes. It results in a low (10%–20%) chance of conception, even after successful diagnosis and treatment [68]. Genital tuberculosis also causes menstrual cycle problems, including secondary amenorrhea and oligomenorrhea, in up to 40% of these patients [70].

Tuberculosis in Pregnancy

There are no studies to our knowledge that have systematically assessed the direct relationship of pregnancy and the risk of tuberculosis [71]. However, conflicting evidence has been reported in the published literature, during both the pre- and postantibiotic treatment eras [72]. HIV infection was reported as a significant trigger of tuberculosis during pregnancy [72], and pregnant women living with HIV have a >10-fold higher risk of developing active tuberculosis than HIV-negative pregnant women [73]. Two studies from Kenya and Rwanda reported that recent pregnancy was a risk factor for the development of active tuberculosis in women living with HIV [74, 75], whereas a study from the Dominican Republic failed to detect an increased risk of active tuberculosis related to recent pregnancy regardless of HIV [76]. Pregnancy can mask the clinical manifestations of tuberculosis, as some of the symptoms of tuberculosis such as fatigue and loss of appetite are also common in pregnancy itself [77, 78].

Several reports showed that pregnant women with untreated tuberculosis, including those living with HIV, have poor obstetric and perinatal outcomes [78]. Pulmonary tuberculosis was associated with an approximate 2-fold increase in premature birth, neonates that are low birth weight and small for gestational age, and a 6-fold increase in perinatal deaths [79]. Similarly, with the exception of tuberculosis lymphadenitis, extrapulmonary tuberculosis has adverse outcomes for pregnancy including increased antenatal hospitalization and neonatal complications [80].

The effects of tuberculosis among pregnant women living with HIV include 2.5-fold increased risk of vertical transmission of HIV [81] and a 2.2–3.2-fold and 3.4-fold increase in maternal and infant mortality, respectively, compared with HIV-negative women [82, 83]. Although tuberculosis is reported to cause 6%–10% of all maternal mortality from both direct and indirect obstetric causes in low HIV prevalence settings, its contribution increases to 15% in high HIV prevalence settings [83–85]. It caused 15%–34% indirect obstetric maternal mortality [83–86]. Undiagnosed active tuberculosis is common among pregnant women and can range up to 11% among women living with HIV [87].

Prevention of Tuberculosis Among Pregnant Women

IPT for 6 months and earlier initiation of ART are the mainstay of tuberculosis prevention among pregnant women living with HIV [36, 41]. For those with confirmed, probable, or possible tuberculosis disease, IPT reduces the overall risk of developing tuberculosis by 33% (relative risk [RR], 0.67; 95% confidence interval [CI], .51–.87). The reduction increased to 64% (RR, 0.36; 95% CI, .22–.61) in patients with a positive TST [88]. Observational studies showed that ART reduces the individual risk of tuberculosis by 54%–92% [89]. Studies conducted in Brazil and South Africa have shown up to 90% reduction in the risk of contracting tuberculosis among people living with HIV with a positive TST who received both ART and IPT [90, 91]. Assessing whether a similar additive benefit could occur among pregnant women remains to be addressed.

IPT is also recommended for pregnant women who are at risk for progression from latent infection to disease, mainly in low tuberculosis prevalence settings. Pregnant women who have likely been infected recently should receive IPT as soon as possible after exposure, even during the first trimester, to prevent the hematogenous spread of *M. tuberculosis* to the placenta. For pregnant women with less likelihood of progression to active disease, IPT can be deferred until after delivery [92]. Isoniazid is not teratogenic even when used in the first 4 months of pregnancy [78], which implies that it can be given at any stage of pregnancy. However, there are reports suggesting an increased risk of isoniazid-associated hepatitis when the drug is administered to pregnant women during the third trimester and the immediate postpartum period or when it is used concomitantly with the administration of acetaminophen [92].

TSTs and IGRAs are available methods to diagnose latent tuberculosis infection among pregnant women. However, none of these tests should be used to diagnose active tuberculosis disease [35]. One study showed that a positive IGRA result during pregnancy in women living with HIV was associated with increased risk of active tuberculosis and mortality during the postpartum period [93]. A simple clinical algorithm recommended by the WHO and based on absence of current cough, fever, weight loss, and night sweats can reliably exclude active tuberculosis disease among people living with HIV [36, 94]. The application of this algorithm among 800 pregnant women in India has resulted in a negative predictive value of 99.3%. TST and targeted chest radiography provided no substantial benefit [95]. Lack of referral for treatment evaluation after TST was one of the main reasons for 30% of attrition of IPT among 730 non–US-born pregnant women [96]. The 4-symptom clinical algorithm should be applied regularly so that it will be possible to

capture those few pregnant women who may present with subclinical disease, which is believed to eventually progress into full-blown tuberculosis disease [97].

Diagnosis of Tuberculosis Among Pregnant Women

There is no difference in the diagnostic approach between men and women, and, as discussed above, current diagnostic tools for tuberculosis rely on AFB microscopy, culture growth, and molecular DNA detection (eg, Xpert MTB/RIF test) of *M. tuberculosis* mainly in sputum. However, women may be less likely than men to submit good-quality sputum [98]. Better quality of sputum and smear positivity was obtained among women by the provision of brief instructions on sputum submission [99]. Classical symptoms of tuberculosis such as cough, sputum expectoration, and hemoptysis are less common among women than men and result in health system delay in the diagnosis of tuberculosis among women [100].

Clinical diagnosis of tuberculosis may be difficult, especially among pregnant women, because of similarities of the nonspecific symptoms related to the physiological response to pregnancy [72]. The majority of tuberculosis in pregnancy is diagnosed during the third trimester [73, 83]. Similarly, the diagnosis of active tuberculosis disease in women living with HIV is not easy because of the presence of fewer bacilli in their sputum [21]. Diagnosis of tuberculosis in most resource-constrained settings still depends on microscopy. HIV infection compromises the validity and effectiveness of chest radiography in the diagnosis of pulmonary tuberculosis. Normal chest radiographs were found in up to 14% of HIV-infected persons who have culture-confirmed pulmonary tuberculosis [21]. In addition, concern about radiation may limit the use of chest radiography during pregnancy. However, it remains an important adjunct in the diagnosis of tuberculosis and should be used among pregnant women with adequate precautions to prevent radiation exposure. The Xpert MTB/RIF test detects tuberculosis cases twice more effectively than smear microscopy without significant difference in performance by sex or HIV status [101]. Its use is recommended by the WHO as the initial diagnostic test in individuals with suspected MDR tuberculosis or with HIV-associated tuberculosis [102].

Treatment of Tuberculosis in Pregnant and Breastfeeding Women

There is no difference in the treatment of tuberculosis among male and female patients. The recommended treatment for women newly diagnosed with pulmonary and extrapulmonary tuberculosis is a daily regimen for 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol (intensive phase), followed by 4 months of isoniazid and rifampicin (continuation phase). This recommended regimen is safe to use during pregnancy [54], and maternal exposure to these drugs showed no risk of congenital abnormality in a large population-based study [103]. Pyridoxine supplementation is recommended for all pregnant or breastfeeding women taking isoniazid. Similarly, vitamin K should be administered at birth to the infant of a mother taking rifampicin because of the risk of postnatal hemorrhage.

Streptomycin is contraindicated during pregnancy because of damage to the eighth cranial nerve that results in ototoxicity ranging from a minor defect of high-frequency hearing loss to bilateral deafness of the fetus [78]. Breastfeeding women should also receive a full course of tuberculosis treatment, and contracting tuberculosis should not be a reason to discontinue breastfeeding. Prompt initiation of tuberculosis treatment of the mother during both pregnancy and breastfeeding is the best way to prevent transmission of *M. tuberculosis* to the newborn. After active tuberculosis in the infant is ruled out, the infant should be given 6 months of IPT, followed by BCG vaccination [54].

Treatment of MDR tuberculosis with second-line tuberculosis drugs during pregnancy was reported with good outcomes for the mothers and without recorded congenital anomalies to the children [104, 105]. The recommended MDR tuberculosis treatment regimen should include 4 second-line anti-tuberculosis drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, in the intensive phase of at least 8 months' duration. The total duration of treatment of MDR tuberculosis should be at least 20 months in patients without any previous MDR tuberculosis treatment [106]. Women with HIV-associated tuberculosis, including those diagnosed with MDR tuberculosis, should receive ART as soon as possible, regardless of their CD4 cell count [57].

URGENT POLICY, PROGRAM, AND RESEARCH ACTIONS

Tuberculosis prevention, diagnosis, and treatment interventions are low cost and high impact [2] and should be integrated into maternal, neonatal, and child health services, depending on the epidemiology of HIV and tuberculosis and the local health system context. Such efforts should primarily be owned by national or subnational government structures and should build on effective collaboration and joint planning between programs responsible for tuberculosis control and maternal, neonatal, and child health services. In particular, national tuberculosis control programs in settings with a high burden of tuberculosis and HIV should reach out to maternal, neonatal, and child healthcare services to ensure the mainstreaming of tuberculosis prevention, diagnosis, and treatment.

The following are the key actions suggested to address the impact of tuberculosis on maternal, neonatal, and child health through integrating tuberculosis prevention and care services (Table 4):

Table 4. Key programmatic actions to address the impact of Tuberculosis on maternal neonatal and child health.

Integrated management of pregnancy and child health services
• Include Tuberculosis prevention, diagnosis and treatment as core component of the integrated management of pregnancy and child health package.
• Tuberculosis prevention, diagnosis and treatment should be included as key interventions at all stages of pregnancy, neonatal, postpartum and postnatal care, particularly in high HIV and Tuberculosis prevalence settings.
Prevention of mother to child HIV transmission services
• Include a sample clinical Tuberculosis screening algorithm that relies on the absence of current cough, fever, weight loss and night sweats in prevention of mother to child transmission of HIV services to identify eligible pregnant women living with HIV for IPT
• Pregnant women living with HIV should be screened regularly using the algorithm at each of their encounters with health workers and based on the outcome of the screening should either be provided IPT or investigated further for Tuberculosis.
• Facilitate the implementation of the integrated patient monitoring system of HIV (pre-ART and ART), PMTCT and Tuberculosis care recommended by WHO, UNICEF and the GLOBAL Fund to Fight AIDS, Malaria and Tuberculosis with standardised indicators.
• Integrated management of childhood illnesses services strengthen the inclusion of Tuberculosis prevention, diagnosis and treatment in integrated management of childhood illnesses for children less than five years old.
Family planning and infertility services
• Include Tuberculosis prevention, diagnosis and treatment services to family planning and infertility services.
• Establish effective referral mechanisms with Tuberculosis services if inclusion is not possible
Tuberculosis and HIV programme services
• Improve the recording and reporting of Tuberculosis data disaggregated by sex and age.
• Encourage the use of case-based electronic recording and reporting systems and mobile phones and other e-health communications and processes.

Integrated management of pregnancy and child health (IMPAC)

Key interventions to improve maternal and newborn health and survival that need to be delivered through health services, the community, and the family are packaged as IMPAC [107]. Tuberculosis prevention, diagnosis, and treatment should be included as part of these key interventions at all stages of pregnancy, neonatal, postpartum, and postnatal care, particularly in high HIV and tuberculosis prevalence settings. The systematic inclusion of tuberculosis prevention, diagnosis, treatment, and care into these services will reduce the associated maternal and infant mortality and improve obstetric and neonatal outcomes.

Prevention of mother-to-child HIV transmission (PMTCT) services

Tuberculosis screening using a simple clinical algorithm that relies on the absence of current cough, fever, weight loss, and night sweats should be used to identify eligible pregnant women living with HIV for IPT. Pregnant women living with HIV should be screened regularly using this clinical algorithm at each of their encounters with health workers. Earlier detection, prevention, and treatment of tuberculosis will reduce the vertical transmission of HIV. Prevention of vertical HIV transmission services should facilitate the implementation of the integrated patient monitoring system of HIV (pre-ART and ART), PMTCT, and tuberculosis care recommended by WHO, United Nations Children's Fund, and the Global Fund to Fight AIDS, Tuberculosis, and Malaria with standardized indicators [108].

Integrated management of childhood illnesses (IMCI)

IMCI is an integrated approach to child health that focuses on the well-being of the whole child and aims to reduce death, illness, and disability and to promote improved growth and development among children <5 years of age. The inclusion of tuberculosis prevention, diagnosis, and treatment as part of IMCI has to be strengthened to raise the level of suspicion of health workers to detect tuberculosis promptly—early in the course of the disease—particularly in HIV-prevalent settings, and existing country experiences should be nurtured [109]. Particular emphasis should be given to infants in whom tuberculosis can present as acute pneumonia, particularly in children living with HIV [24].

Family planning and infertility services

Tuberculosis diagnosis and treatment should be integrated into existing family planning services, or effective referral mechanisms should be established to enhance the diagnosis of tuberculosis among women of reproductive age. Genital tuberculosis should be considered as a differential diagnosis for infertility in high tuberculosis prevalence settings.

Improvement of surveillance and reliable data generation

The exact extent of drug-susceptible, drug-resistant, or HIV-associated tuberculosis in children and women, including pregnant women, should be improved through more reliable diagnosis and reporting of cases and analysis of data disaggregated by age. One can not underemphasize the importance of rapid, simple, and accurate point of care tuberculosis diagnostics, not only to improve the care given to mothers and children but also to improve reliable routine data generation through better case ascertainment. Allowing the inclusion of children in all tuberculosis prevalence surveys would be a major step forward toward better understanding of the burden; however, logistical and practical hurdles will exist until a simple and accurate point-of-care test is available. Routine source of data on mortality should be obtained from a vital registration system that assures permanent, compulsory, and universal recording of the occurrence and characteristics of vital events such as births, deaths, and causes of deaths. There have been recent efforts to improve the use of vital registration systems to improve the estimates of tuberculosis mortality [1], and these efforts should be further expanded to include reliable data on women of reproductive age and children. The use of case-based electronic recording and reporting systems, mobile phones, and other electronic health

communications and processes should also be encouraged. In the meantime, it is also important to enhance the analysis of existing data at the facility level to inform policy and program performance at local and national levels.

Addressing unmet research needs

The absence of an effective vaccine, drugs allowing shorter duration of treatment, and a rapid and simple point-of-care tuberculosis diagnostic tool to accurately diagnose all forms of tuberculosis calls for massive basic and operational research investments. These research needs have been described elsewhere [110–113]. However, it should be emphasized that ongoing basic and operational research efforts should always ensure that the needs of children and pregnant and breastfeeding women are addressed. Basic research on diagnostics needs to identify simple point-of-care tuberculosis diagnostic tools that do not rely on sputum only (eg, dipstick tuberculosis test) to improve childhood and maternal tuberculosis diagnosis and care. Drug discovery research needs to include pregnant and breastfeeding women and children, including those living with HIV, as early as possible in the anti-tuberculosis drug development pipeline. Tablets of fixed-dose drug combinations have several advantages over individual drugs, including less likelihood of prescription errors and lesser pill burden, particularly for children, and efforts to yield effective fixed-dose drug combinations are needed.

CONCLUSIONS

The evidence presented in this review illustrates that tuberculosis is one of the major public health concerns for women of reproductive age, pregnant women, and children. Mortality and morbidity implications are a huge toll, particularly in resource-constrained settings with high tuberculosis and HIV prevalence. National policy makers, program managers, and international stakeholders (eg, United Nations bodies, donors, and implementers) working on maternal, neonatal, and child health, especially in HIV-prevalent settings, should give due attention to and include tuberculosis prevention, diagnosis, and treatment services as part of their core functions and address the public health impacts of tuberculosis in their programs and services.

Notes

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