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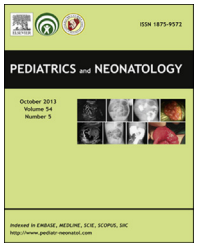

REVIEW ARTICLE

Childhood Tuberculosis: Epidemiology, Diagnosis, Treatment, and Vaccination

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Despite the existence of a government-run tuberculosis (TB) control program, the current nationwide burden of TB continues to be a public health problem in Taiwan. Intense current and previous efforts into diagnostic, therapeutic, and preventive interventions have focused on TB in adults, but childhood TB has been relatively neglected. Children are particularly vulnerable to severe disease and death following infection, and children with latent infections become reservoirs for future transmission following disease reactivation in adulthood, thus fueling future epidemics. Additional research, understanding, and prevention of childhood TB are urgently needed. This review assesses the epidemiology, diagnosis, treatment, and relevant principles of TB vaccine development and presents efficacy data for the currently licensed vaccines.

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1. Introduction

Tuberculosis (TB) is prevalent in poor and marginalized populations, although human immunodeficiency virus (HIV) infection is another major driver of the epidemic in certain areas.[1] Poor case ascertainment and limited surveillance data hamper the efforts to accurately quantify the disease burden associated with childhood TB.[2] Childhood TB contributes approximately 15–40% of all TB cases.[3–5] Childhood TB is usually acquired from an infectious adult contact. High rates of transmission are sustained in TB-endemic areas due to high case density and prolonged diagnostic delay.[6] As childhood TB reflects ongoing transmission, children are affected most acutely in areas where an adult TB epidemic is poorly controlled.[7] The global TB control strategy has focused predominantly on smear-positive cases and, therefore, not on childhood TB, which is usually paucibacillary and smear negative.[3] In addition, childhood TB remains neglected for various reasons, mainly the difficulty in diagnosing pulmonary TB, the lack of scientific studies on childhood TB, the largely unknown outcomes of children with TB, and the belief that childhood TB is not important for TB control.[3,8] Although nearly 11% of all global TB cases occur in children less than 15 years of age,[7] childhood TB is not prioritized by national control programs because children contribute little to transmission. Moreover, children in TB-endemic areas suffer severe TB-related morbidity and mortality, and a large proportion of cases are diagnosed solely on the basis of medical history and clinical examination.[2,3] Further research, understanding, and prevention of TB among children are urgently needed. The purpose of this review is to explore the epidemiology, diagnosis, treatment, and relevant principles of TB vaccine development and to present efficacy data for the currently licensed vaccines.

2. Epidemiology

2.1. Global childhood TB

The World Health Organization (WHO) estimates that of the approximately 8.3 million new cases of TB diagnosed in 2000, 10% were children less than 15 years of age.[3] During 2008, an estimated 9.4 million new TB cases were diagnosed, with most cases living in Africa and Asia,[1] but no estimates of childhood TB were included. In a prospective community-based survey performed in an area of South Africa, children less than 13 years of age contributed 14% of the total TB disease burden, with an annual incidence of 408/100,000.[9] More recent estimates suggest that children less than 15 years of age contribute 10–20% of the disease burden in TB-endemic areas.[10] From these informal observations, it is evident that children with TB are frequently misdiagnosed in TB-endemic areas, and we are currently only witnessing a small piece of the overall picture with the bulk of cases passing undetected. The misperception that children with TB rarely develop serious disease was based on data from developed countries where diligent contact tracing and active case finding ensure that children are diagnosed early in their disease course. By contrast, children in developing countries have a 20-fold greater risk for TB disease than HIV-uninfected children and are at much higher risk of TB-related death.[11]

2.2. Childhood TB in Taiwan

We analyzed data obtained from the Taiwan Tuberculosis Control Report, which was published by the Center for Disease Control (Taiwan CDC).[12] The data indicated that the proportion of childhood TB among all TB cases ranged between 0.72% and 1.24% during the data collection period (2002 and 2009) (Table 1). The number of childhood TB cases detected each year was relatively small. The overall annual incidence rate during the entire data collection period was 3.04 and 82.60 per 100,000 population for children and adults, respectively. For children, there was a 46% decrease in the incidence of TB, a decrease from 4.82/100,000 population in 2002 to 2.60/100,000 population in 2009 (Chi-square test for the linear trend $= 19.3$, $p < 0.001$). For adults, the incidence of TB decreased 31% during the study period from 99.76/100,000 population in 2002 to 68.80/100,000 population in 2009 (Chi-square test for the linear trend $= 5.8$, $p = 0.016$) (Table 1).

The annual incidence by age group presented a decline in the most recent years, demonstrating a peak incidence rate in the 10–14 year age group (3.63 per 100,000 population), followed by the 0–4 year age group (3.18 per 100,000), and the 5–9 year age group (2.27 per 100,000) (Figure 1A). Overall, childhood TB incidences in all age groups were highest in 2002 and decreased in the following years.

The annual incidence rates by gender are shown in Figure 1B. Females had higher incidence rate than males (3.18 vs. 2.91 per 100,000 population; Chi-square $= 3.96$, $p = 0.03$).

The childhood incidence rate by region is shown in Figure 2. The incidence pattern was different among the four regions studied between 2002 and 2009. The eastern region had the highest rate of all of the studied regions (16.2 per 100,000), followed by the southern region (3.00/100,000), the northern region (2.39/100,000), and the central region (1.93/100,000). The adult incidence rate by region was as follows: the eastern region (127.24 per 100,000), the southern region (88.50/100,000), the central region (72.56/100,000), and the northern region (64.37/100,000).

Table 1 Proportion of childhood tuberculosis (TB) cases among all TB cases and annual incidence of TB in children and adults in Taiwan, 2002–2009.

Year	Total no. of cases*	No. of cases (%) in children	Annual incidence†	
			Children	Adults
2002	18,013	223 (1.24)	4.82	99.76
2003	14,074	122 (0.87)	2.69	77.41
2004	17,142	140 (0.82)	3.16	93.50
2005	16,472	118 (0.72)	2.73	88.85
2006	15,378	114 (0.74)	2.71	81.97
2007	14,480	115 (0.79)	2.81	76.29
2008	14,265	112 (0.79)	2.82	74.37
2009	13,336	100 (0.75)	2.60	68.80
Total	123,160	1044 (0.85)	3.04	82.60

* Includes the number of cases in children and adults.
† Expressed by cases per 100,000/year.

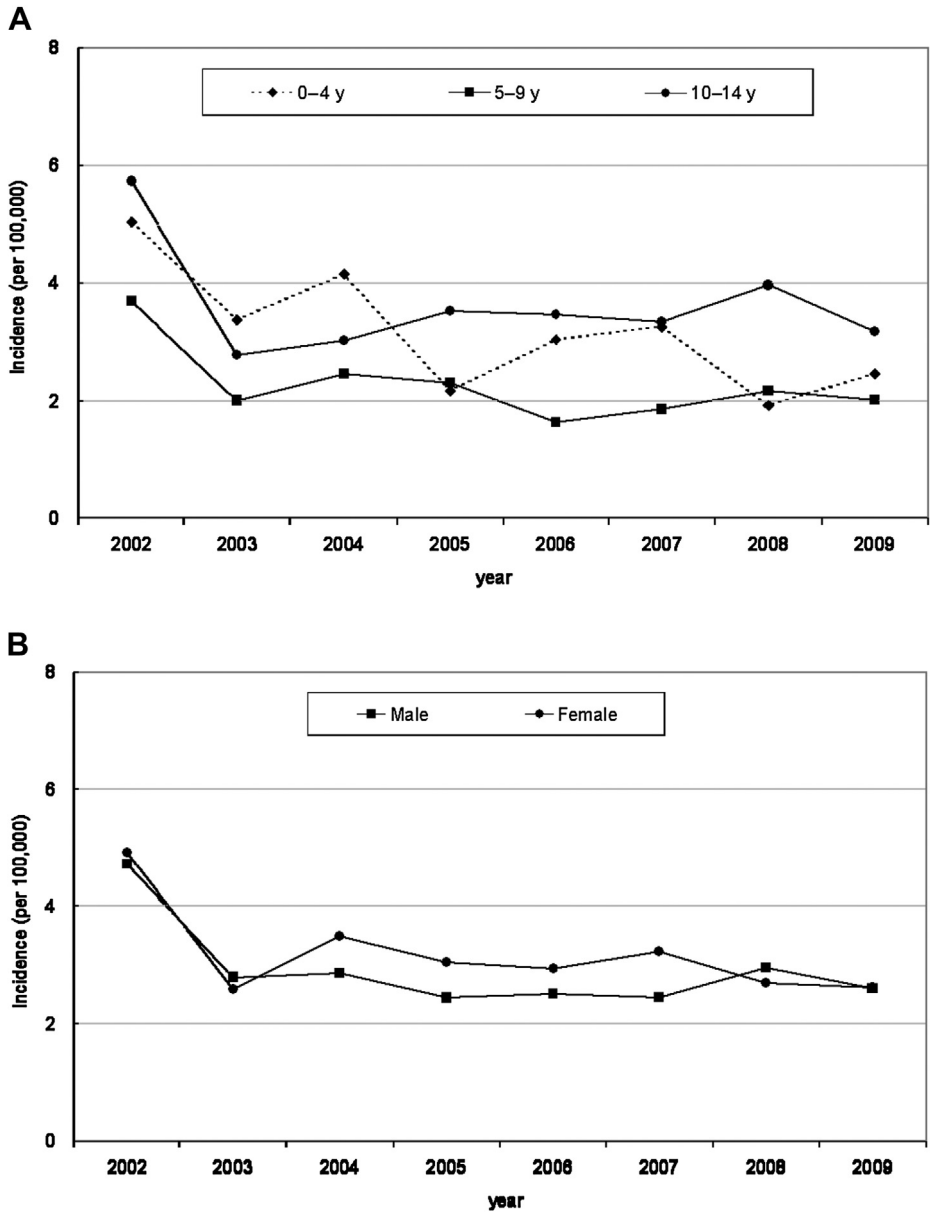

Figure 1 Annual incidence of tuberculosis (TB) in children under 15 years old by age group (A) and gender (B) in Taiwan, 2002—2009.

3. Diagnosis of TB

Diagnostic difficulties pose the greatest challenge to childhood TB management. TB can mimic many common childhood diseases, including pneumonia, generalized bacterial and viral infections, malnutrition, and HIV infection. However, the main impediment to the accurate diagnosis of active TB is the paucibacillary nature of the disease in children.[13] Younger children also produce smaller amounts of sputum, which is usually swallowed rather than expectorated. Consequently, bacteriological confirmation is the exception rather than the rule, with only 10—15% of sputum samples revealing acid-fast bacilli (AFB) and sputum cultures remaining negative in approximately 70% of cases with probable TB.[14] The diagnosis of TB is usually based on exposure history, clinical features, tuberculin skin test (TST), and chest radiography.[15,16]

3.1. Clinical features of disease

Fever and/or cough of recent onset lasting longer than 2 weeks should arouse suspicion of TB.[17] Fever can be of any type, and the often-described evening rise of temperature is neither specific to this etiology nor commonly present. The cough can be dry or moist and may be severe. A cough persisting beyond 2 weeks, particularly as the only symptom in an otherwise healthy child, can be due to asthma and is often not due to TB. A recent loss of appetite may be relevant, but the unexplained recent loss of weight can be an important symptom suggesting TB. A history of contact

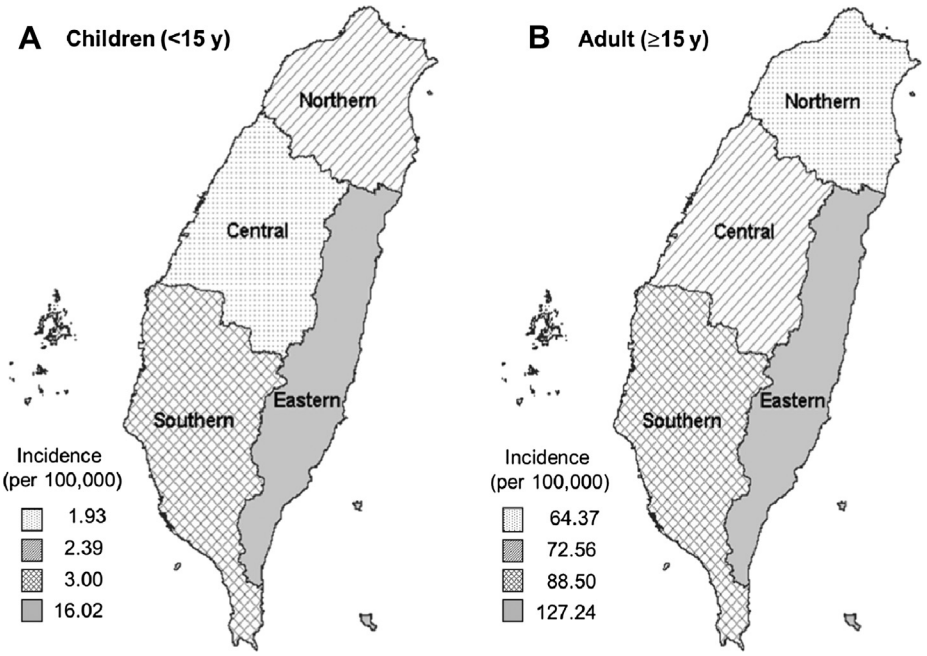

Figure 2 Annual incidence of tuberculosis by region in Taiwan, 2002—2009: (A) in children under 15 years old; (B) in adults.

with a smear-positive TB patient should always prompt a detailed examination for the disease. Persistent lower respiratory infection that is not responsive to antibiotic therapy may indicate a probable TB diagnosis. Significant superficial lymphadenopathy should be specifically sought, as it often coexists with TB infection.

3.2. Tuberculin skin test

The Mantoux test is the recommended standard tuberculin test.[18] Tuberculin is commercially available in 1, 2, and 5 Tuberculin Unit (TU) PPD (purified protein derivative, RT23 equivalent) forms.[19,20] For the test, it is important to raise a wheal of approximately 6 mm after the intradermal injection. The test is read 48—72 hours after an injection. Ballpoint or palpatory methods are used to read the induration. A prior Bacillus Calmette-Guérin (BCG) vaccine may influence the PPD reaction depending on conditions such as the interval between BCG vaccination and TST and the age at vaccination.[21] If the prevalence of TB infection is high enough, the positive predictive value of TST would be higher.[22] If the patient returns for a reading beyond 72 hours but before the 7th post-injection day, a positive test can still be read. A repeat test may be needed if there is no induration and the wheals present beyond the stipulated time for reading. A repeat tuberculin test, when required, should preferably be performed on the other arm.

3.3. Chest radiography

There are no pathognomonic radiological signs of TB. Chest radiography merely localizes the site of pathology and does not confirm etiology.[23] In relevant clinical settings, certain radiological lesions may strongly suggest TB. These lesions include miliary, hilar, and paratracheal lymphadenopathy with or without parenchymal involvement and fibrocaseous cavitatory lesions. In clinical practice, nonresolving chest shadows following adequate antibiotic therapy in a symptomatic child raise the possibility of TB. It is worth mentioning that not all persistent radiological lesions are necessarily due to TB. Asymptomatic patients may have persistent shadows due to parenchymal scarring, pleural thickening, and healed fibroatelectatic changes. However, a child with bronchiectasis or an interstitial lung disease may present with nonresolving shadows with persistent symptoms.

Ultrasonography of the chest is helpful to assess pleural fluid collection, but a decubitus chest X-ray film may also reveal similar information.[23] High-resolution computed tomography (CT) offers excellent anatomical visualization, and low-dose CT for children suspected of having pulmonary TB infection can help in the decision to pursue further antibiotic treatment.[24] However, because of the high cost of CT and the high level of radiation to which the patient is exposed, as compared with other forms of imaging, it should be reserved for complicated cases.[25]

3.4. Bacteriology

A confirmation of AFB from any body fluid or tissue is the gold standard for the diagnosis of TB. Such proof is often lacking in childhood TB cases because of the difficulty in the collection of sputum and because of paucibacillary primary disease in children. However, studies indicate that the positive AFB test yield in advanced childhood cases may be as high as that in adults. Several studies have reported bacteriological positivity rates as high as 33% even for primary disease states, such as hilar adenopathy.[26] Therefore, every attempt must be made to bacteriologically prove the diagnosis in every case of suspected TB. Early morning gastric aspirate is the preferred specimen for most young

children with suspected TB. The aspirate is preferable for both detecting AFB and isolating *Mycobacterium tuberculosis*.[13] Whatever method a clinician uses, he/she needs to collect at least two, preferably three, samples.

A Ziehl-Neelsen stain can reveal AFB only if the sample contains greater than 10,000 bacilli per mL. Different culture methods, such as Lowenstein-Jensen medium, radiometric (Bactec 12B liquid medium), and nonradiometric (Bactec MGIT 960 system), can be used for confirming diagnosis in the paucibacillary state.[27] The newer methods are capable of providing faster results and may be used if available. Mycobacterial culture assumes special significance in cases of suspected drug resistance.[27]

Recent advances in bacteriological and molecular methods to improve TB diagnosis have been described recently. These methods include the microscopic observation drug susceptibility (MODS) test,[28] more sensitive pulmonary computed tomography (PCT) techniques,[29] or phage-based tests.[30] However, although several studies on diagnostic accuracy of these methods in adults were published with considerably heterogeneous results, very few data are available on children. In December 2010, the Xpert MTB/RIF assay ("Xpert", Cepheid Inc., Sunnyvale, CA, USA) was endorsed by the WHO for direct TB screening on sputum samples.[31] The Xpert MTB/RIF assay is less sensitive than liquid cultures for the detection of *M. tuberculosis* in both children and adults; it provides results quickly, is highly specific, and detects resistance to rifampin.[31]

3.5. Interferon Gamma Release Assays (IGRAs)

In addition to the traditional TST, which is known to lack both sensitivity and specificity, blood-based assays have recently become available. These T-cell assays rely on the stimulation of host blood cells with *M. tuberculosis*-specific antigens and measure the production of interferon γ. Several studies have compared the two available commercial assays, T-Spot TB (Oxford Immunotec, Abingdon, UK) and Quantiferon-TB Gold (Cellestis, Carnegie, Australia), with the TST for both the detection of active disease and latent TB infection.[32] The T-cell assays have proven to be more specific than the TST but are currently unable to distinguish between active disease and latent TB infection.[32] Therefore, interpretation of the results remains dependent on the clinical context. Several studies have presented pediatric T-cell assay data; however, none have provided an assessment of age-related performance, and reservations remain regarding their performance in very young children and immunocompromised populations, such as those with HIV infection.[33] The costs and technical demands of IGRAs will most likely limit their wider use in resource-poor settings where better tests are most needed.

3.6. PCR testing

Nucleic acid amplification tests using polymerase chain reaction (PCR) cannot differentiate living bacilli from dead bacilli. Thus, these tests continue to give positive results even after successful treatment. The PCR tests are positive in 95—100% of culture-positive cases and in 50—60% of culture-negative cases.[34] Over the past several decades, the diagnostic methods for *M. tuberculosis* have improved, and nucleic acid amplification techniques now allow rapid and sensitive detection in the clinical setting.[35]

4. Treatment of TB in Children

The principles of TB treatment are the same for adults and children. The combination regimens used to treat active disease aim to eliminate actively replicating and dormant or near-dormant mycobacteria using a combination of minimum-toxicity drugs with different actions while preventing the emergence of drug-resistant organisms.[36]

TB treatment consists of two phases: an intensive phase with a combination of bactericidal drugs to kill the rapidly growing bacilli and a continuation phase with fewer drugs to eradicate the slower-growing persistent bacilli.[36] The adjunctive use of steroids in TB meningitis has been shown to reduce death and severe disability.[37]

Fixed-dose combination tablets contribute to increased adherence to treatment regimens, but the marked differences in absorption, distribution, and excretion of pharmacological agents in children of various ages might require dose adjustments.[38] Table 2 lists the regimens by disease category as currently recommended by the WHO,[36,38] and Table 3 lists the regimens by disease category as currently recommended by the Taiwan CDC.[39] A number of pharmacokinetic (PK) studies in children indicate that age is a determinant of serum levels for all the first-line anti-TB drugs and that infants and young children have lower peak serum levels than older children or adults.[36,40,41] The revised recommended dosages are listed in Table 4.

4.1. Drug-resistant TB

Poor patient compliance to anti-TB therapy is the major contributory factor to the failure of a TB control program and has increasingly led to drug resistance.[38] The rates of drug resistance to any drug vary from 20% to 80% in different geographic regions.[38,42]

Resistance should be suspected if an index case has known resistant TB, if the child demonstrates initial improvement on anti-TB treatment and then deteriorates, or if there is no response to the initial treatment. Acquired resistance is well described in HIV co-infected adults, possibly resulting from a higher proportion of drug-resistant strains in endemic areas, decreased absorption of oral antimycobacterial drugs among HIV-infected persons, or other factors.[43] The presence of acquired resistance in the pediatric population has also been reported; in particular, children with HIV/TB co-infection should be closely monitored.[44]

The current guidelines recommend using at least four patient-naïve drugs, including an injectable and a fluoroquinolone, in an initial phase for at least 6 months. The initial phase should be followed by the use of at least three of the most active and best-tolerated drugs in a 12—18 month continuation phase. Standardized regimens have been developed for settings where drug susceptibility testing is not available.[45] Six classes of second-line drugs are available, but research on the use of these drugs in

Table 2 Treatment regimens for children recommended by WHO.[36,38]

Category of treatment	Category of TB cases	Anti-TB drug regimens	
		Intensive phase	Continuation phase
I	**New patient regimen** New smear-positive PTB Smear-negative PTB with extensive parenchymal involvement Severe forms of EPTB other than TB meningitis	2HRZE	4HR
II	**New patient regimen** Smear-negative PTB without extensive parenchymal involvement Less severe forms of EPTB (e.g., TB cervical adenitis)	2HRZ	4HR*
III	**New patient regimen** TB meningitis	2HRZS†	4HR
IV	**Retreatment regimen** Previously treated smear-positive PTB (relapse, treatment after interruption or treatment failure) *If low risk for MDR-TB or risk unknown, continue with retreatment regimen* *If high risk for MDR-TB, use MDR-TB regimen below*	2HRZES/1HRZE	5HRE
V	**MDR regimen** MDR-TB	Individualized regimens	

E = ethambutol; EPTB = extrapulmonary tuberculosis; H = isoniazid; HIV = human immunodeficiency virus; MDR-TB = multidrug-resistant tuberculosis; PTB = pulmonary tuberculosis; R = rifampicin; S = streptomycin; Z = pyrazinamide; WHO = World Health Organization.

* 2HRZ 4HR denotes a 2-month intensive phase of daily isoniazid, rifampicin, and pyrazinamide followed by a 4-month continuation phase of daily isoniazid and rifampicin.

† Other regimens are recommended for treatment of TB meningitis that include replacing streptomycin with ethionamide and treating for 9–12 months.

children is limited, and multicenter pediatric trials are needed.[45] Under optimal circumstances, multidrug-resistant TB responds well to appropriate therapy. However, delays in diagnosis and treatment, adherence issues, and a lack of child-friendly formulations and strategies for directly observed treatments (DOTS) frequently complicate management and contribute to high morbidity and mortality.[46]

Table 3 Treatment regimens for children recommended by the Center for Disease Control (CDC) Taiwan.[39]

Category of disease	Anti-TB drug regimens	
	Intensive phase	Continuation phase
PTB, mild EPTB	2HRZ	4HR*
Severe EPTB	2HRZ	7–10HR
TB meningitis	2HRZA or 2HRZP	7–10HR
MDR	Individualized regimens	
HIV infection	2HRZ	7–10HR

A = aminoglycoside; EPTB = extrapulmonary tuberculosis; H = isoniazid; HIV = human immunodeficiency virus; MDR = multidrug resistance; P = prothionamide; PTB = pulmonary tuberculosis; R = rifampicin; Z = pyrazinamide.

* 2HRZ 4HR denotes a 2-month intensive phase of daily isoniazid, rifampicin, and pyrazinamide followed by a 4-month continuation phase of daily isoniazid and rifampicin.

Table 4 First line anti-tuberculosis (TB) drugs for children currently recommended by WHO[36,38] and the Center for Disease Control (CDC) Taiwan.[39]

Drug	Daily dose range (mg/kg)	
	Recommended by WHO	Recommended by Taiwan CDC
Isoniazid	10–15	10–15
Rifampicin	10–20	10–15
Pyrazinamide	30–40	15–20
Ethambutol	15–25	15–20
Streptomycin	12–18	20–40
Amikacin		15–30
Kanamycin		15–30
Prothionamide		15–20
Cycloserine		10–20
Para-aminosalicylic acid		150–600
Moxifloxacin		7.5–10

5. Vaccination

Several large-scale randomized clinical trials in different settings worldwide have suggested a protective efficacy from BCG vaccination against pulmonary TB that ranges from 0% to 80%.[47] The variability in vaccine efficacy has been attributed to several factors, including strain-specific immunogenicity, technique of vaccine administration, age at vaccination, genetic differences between populations, host nutritional factors, host co-infection by parasites, exposure to environmental mycobacteria, and genetic variation in *M. tuberculosis* strains. However, the greatest effect of BCG vaccination seems to be in preventing severe disseminated disease in young children, including TB meningitis and miliary TB.[47] The longevity of protection is less clear. A meta-analysis of early trials suggested that protective immunity lasts less than 10 years; however, more recent data suggest that protection could persist for 50—60 years.[48,49]

The WHO guidelines recommend administration of BCG soon after birth to all infants in countries with high TB prevalence.[50] To date, the efficacy of BCG vaccination has not been determined in HIV-infected individuals in whom the immune responses to the vaccine could be reduced,[51] although this topic is the focus of ongoing trials. Because of the risk of disseminated BCG disease that might complicate the use of this live vaccine in immunocompromised individuals, BCG vaccination is not recommended in children known to be infected with HIV infection in low-TB prevalence countries.[50,51]

Given the proven efficacy of the existing BCG vaccine in preventing disseminated TB in children and reducing child mortality, two conceptually different strategies are being pursued.[49] First, the development of priming vaccines, which, it is hoped, will replace BCG by providing better and longer-term protection. Second, researchers are pursuing the design of booster vaccines to boost pre-existing BCG-derived immunity. All of the novel vaccines currently under development use a booster strategy following priming with BCG in infancy. Such a vaccine could be used as a booster vaccine with the goal of preventing new infections in those uninfected with *M. tuberculosis* and to prevent reactivation in those with latent TB infection.

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