CHAPTER 1.4

CHILDHOOD TB: IMPLICATIONS FOR NEW TB VACCINES

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The short and brutish life of millions of street children expose them to drugs, violence, rape, humiliation and several diseases and, in areas of armed conflicts, many of them end their lives as children of war.

‘The world is not magic anymore, you have been left alone.’

1964
Jorge Luis Borges

‘Pepito Malecon’
From the series Happiness and Sadness from Malecon
Pedro Pablo Oliva
Oil on canvas; 200 × 250 cm
EPIDEMIOLOGY OF CHILDHOOD TB

There were 8.8 million incidents of TB cases and a total of 1.45 million deaths from TB in 2010 (1). Unfortunately, it is not clear how many of these cases were children, since pediatric tuberculosis is a relatively neglected disease from the global health perspective. Multiple factors conspire to conceal the contribution of childhood TB to the global epidemic and the burden of TB-related morbidity and mortality that is borne by infants and children. Accurate surveillance of childhood TB disease is hampered by the non-specific nature of symptoms, which may be similar to those of other childhood infections in developing countries with high levels of poverty and malnutrition, the difficulty in collecting respiratory specimens for microbiological confirmation, and the pauci-bacillary nature of TB disease in children (2). Ultimately, the fact that global TB control measures and policies have traditionally hinged upon data from sputum smear-positive or culture-positive patients, whereas children with TB are often smear-negative and culture-negative, has resulted in a disappointing lack of pediatric epidemiological data to inform national and global TB control programs (1, 3, 4). This lack of focus on childhood TB is particularly regrettable, since children have higher risk of progression from infection to disease, coupled with higher risk of progression to severe morbidity and death, compared to adults (5, 6). Infected children act as a reservoir for future adult reactivation disease, but more importantly, since adults usually infect young children, each new case of childhood TB acts as a sentinel for an adult infectious TB case in the household or community. TB transmission to children is a function of contact duration, proximity, and infectiousness of the source case, as well as the age, nutritional status, immune status, and vaccination status of the exposed child. These risk factors combine to form two peaks in TB incidence, in infancy and adolescence, with a trough during the school age years (7).

Given the lack of programmatic notification data, it is very difficult to estimate the true incidence of childhood TB disease (2, 4, 8–10). It was thought that more than 1 million incidents of child TB cases occurred in 2000, based on the estimate that 10% of the projected 10 million TB cases would have occurred in children younger
than 15 years of age. The World Health Organization (WHO) data indicate that the global TB incidence has continued to fall since 2002, but if the 10% estimate were accurate, we would expect 880,000 children to have developed TB disease in 2010 (4). However, estimates of childhood TB incidence from selected well-resourced countries, with good statistical records, should not be used to predict global burden of childhood TB (4, 11). The clinical and demographic profiles of cases in these countries are likely to be skewed towards the reactivation of the disease in older adults, whereas younger adults of child-bearing age are more likely to expose children to household TB transmission in resource-poor countries, coupled with household over-crowding. It follows that children might constitute less than 5% of TB cases in low prevalence countries, but 20% of cases in high prevalence countries with a younger demographic population. For example, in Europe, childhood TB is largely restricted to immigrant children and children of immigrant parents from Africa and the Indian subcontinents. Six per cent of all TB cases in the USA in 2001 were coming from children (0–14 years), a rate of 1.5 child cases per 100,000 (Centres for Disease Control). By contrast, more than one third of the TB caseload in a South African study have occurred among children younger than 14 years of age (12). The incidence of notified TB disease among children aged 0-5 years in urban Cape Town during the period of 1985–1994 was 3,588 per 100,000, compared to 1,149 per 100,000 in the general population i.e. three-fold higher (12). Children made up 39% of the total average annual TB caseload and up to 58% in some years. This study illustrates that the very high incidence in younger children is partly obscured, since adults contribute more to total caseload due to more years at risk.

The epidemiology of childhood TB has also been impacted by the HIV pandemic (13). The incidence of TB in HIV-infected South African children was 21 per 100 person years of observation in one study, a rate which was approximately 14-fold higher than the incidence among HIV uninfected children (14). The prevalence of drug-resistant TB is also increasing amongst children, with 15% of cases being mono-resistant and 7% of cases multi-drug resistant (MDR-TB) in one recent South African survey (15). However, in contrast to the adult epidemic, HIV infection is not associated with increased risk of drug-resistant TB in children. This may be due to the fact that increased risk of TB in HIV-infected children is not only a function of immune-compromise, but also due to increased risk of household exposure to HIV-infected adults. TB incidence in young children reflects transmission of TB disease among their adult caregivers. Hence, increased rates of TB among adults, driven by the HIV pandemic, will result in increased childhood TB risk in HIV-affected households, independent of whether children are HIV infected or
otherwise (11). However, it may be difficult to make a confident diagnosis of TB in HIV-infected children, since it is difficult to distinguish sputum smear-negative and culture-negative TB from HIV-associated acute and chronic lung disease, such as lymphocytic interstitial pneumonitis (LIP) (13).

It is clear that there are few high TB-burden countries with reliable programmatic, epidemiological data on the incidence and prevalence of childhood TB to direct allocation of health care resources, including resources for possible new TB vaccine programs (4, 8, 9). Planning for multi-centre TB vaccine efficacy trials in infants and children will also need accurate data on local TB case incidence to estimate sample size. Projected accrual of childhood TB disease endpoints will be a critical determinant of study size, duration, and cost for these efficacy trials. Data on paediatric TB incidence rates at potential vaccine efficacy trial sites come from a handful of epidemiological studies and recent Phase IV BCG trials in research settings (16–19). The advantage of using these data to predict childhood TB disease incidence in future efficacy trials is that the data are affected by the same factors that will influence the diagnostic phenotype, clinical severity, and incidence of childhood TB disease in a vaccine trial setting: active surveillance and case-finding in the study population; rigorous radiological and microbiological investigations; isoniazid prophylaxis for documented TB exposure and latent TB infection; and early TB treatment for suspected disease. Therefore, data collected in research settings are likely to be a true reflection of the incidence in future TB vaccine trials. However, the disadvantage of using such data is that TB cases identified using best research practices and optimal resources are likely to be detected at an earlier age, and with milder disease severity than TB cases outside of the study population, even in adjacent communities. It is clear that TB cases in a modern infant vaccine efficacy trial are likely to reflect a different phenotype, with different morbidity and mortality, compared to TB cases reported in routine health care systems (20). It is also clear that the incidence of childhood TB disease is critically dependent on how that TB disease phenotype is defined. Mulenga et al report on 2,185 South African children investigated for suspected TB under vaccine trial conditions (16). Discordance between clinical, radiological, and microbiological diagnostic features is common. For example, one third of children with a chest radiograph compatible with TB, and up to half of children culture-positive for MTB, do not demonstrate any classical symptoms of TB disease at presentation. The annual incidence of culture-confirmed MTB cases in this study population is less than 200 per 100,000. By contrast, the incidence of the diagnostic triad composed of TB exposure (defined as a known adult TB contact, or tuberculin skin test conversion), with compatible symptoms and chest radiograph, was 848 per 100,000 (more than four-fold higher).
SPECTRUM OF MORBIDITY DUE TO CHILDHOOD TB

The huge burden of morbidity, disability, and mortality due to childhood TB was unquestionable in the pre-chemotherapy era. The TB mortality rate in Wales in the mid-19th century was estimated at 600 deaths per 100,000 children. Even in the last century, Lincoln et al. reported mortality in excess of 50% among infants with TB and, in 1963, Miller reported that tuberculous meningitis had developed in 15-20% of infants who converted to positive TST (21–23). By contrast, Van Rie et al. reported on 1,744 child TB cases from a community in Cape Town, South Africa, during a period when triple drug therapy was available (1983–1994) (12). Of the 1,744 child TB cases reported, only 9 children had TBM (0.5%) and a single child died (0.06%). However, a later study from the same community in the period of 2003–2005, included 214 of 1024 child TB suspects <10 years of age (21%) who were diagnosed with TB disease (24). In this study, 6.5% developed disseminated miliary disease; 6.5% with adult-type cavitatory disease; 50% with parenchymal consolidation and/or airway compression; and 36% with intrathoracic lymphadenopathy only. One death (0.05%), of a 3-month old HIV-uninfected child who contracted miliary TB has occurred.

Accurate incidence rates for disseminated TB disease in children are difficult to estimate, since half or more of childhood TBM may not be notified to health authorities, although the rate of TBM was thought to be in the region of 32 per 100,000 in infants in the Western Cape region of South Africa (25). The rate of disseminated TB disease is likely to be even lower in a research setting. In one of the largest cohorts of recent years, 385 cases of algorithm-defined definite or probable TB were observed among almost 12,000 BCG-vaccinated South African infants followed until two years of age (annual incidence 1.6%), but only 4 cases of TBM (annual incidence 0.015%), a single case of miliary TB, and no TB deaths, were observed in this study (17). These data illustrate the changing phenotype of TB disease since the introduction of effective chemotherapy. However, the relative burden of childhood TB, compared to adult disease, remains high. Children are known to have a higher rate of extrapulmonary disease than adults (29% pulmonary and extrapulmonary; 22% only extrapulmonary) (26). In particular, miliary disease and TBM are more common in children than among adults, since disseminated disease is an early complication of primary infection, and it is estimated that 71% of all miliary disease and 80% of all TBM is found in young children (27).
Marais and colleagues have provided excellent reviews of the natural history and epidemiology of TB disease in the pre-chemotherapy era, describing a series of historical studies that each followed 1,000 or more children for 10 years or longer (5, 6). In these studies, primary TB infection before the age of two years frequently progressed to serious disease within 12 months of infection, without significant prior symptoms. By contrast, primary infection between the ages of 2–10 years rarely progressed to serious disease; and such progression was usually associated with significant symptoms, which represented an opportunity to establish a clinical diagnosis prior to the development of severe morbidity and mortality. The vast majority of TB disease manifestations occurred in the 6–12 months following primary infection documented by the TST conversion. Overall, 50–70% of children demonstrated radiological evidence of intrathoracic lymph node enlargement following primary infection (primary complex TB), irrespective of the presence or absence of symptoms, but 70% of lesions cleared within one year. The prognosis of primary infection was also age-dependent, in that infection under two years of age carried a significant risk of progressive disease, even if the CXR was considered normal. Infants younger than one year of age with immature immune systems were at highest risk, developing pulmonary disease in 30–40% of cases, and tuberculous meningitis or military disease in 10–20% of cases. This risk decreased to 10–20% and 2–5%, respectively, in the second year of life. However, 95% of children aged 2–5 years did not progress to disease following primary infection. In these older children, radiological evidence of enlarged intrathoracic lymph nodes was rarely associated with symptoms, such as persistent unremitting cough or wheeze, unless associated with bronchial disease characterized by degrees of airway obstruction and parenchymal involvement. Infants younger than one year had the lowest annual risk of infection (<1%), but the highest age-specific risk of notification with TB disease following infection is diagnosed in 11% and the highest risk of TB-related death following infection is found in 6% of these children (5). By contrast, children who were TST negative at 10 years of age and older were at high risk of developing adult-type cavitating disease following incident primary infection. Therefore, previously uninfected adolescents are especially vulnerable in high-burden communities where the risk of future infection is high. It is notable that, although 60–80% of children younger than two years have developed radiological abnormalities following primary infection, only 5–10% of these children were notified (22, 23). This finding implies that either the notification was omitted in error, or that the majority of children contained the primary complex TB and that it has resolved spontaneously without treatment. It has been suggested that highly
immunogenic new TB vaccines might even cause a paradoxical and misleading increase in the apparent rate of self-curing primary complex TB, on the basis of enhanced reaction of draining lymph nodes following primary infection (19, 28). This is an important point for future infant TB vaccine trials, since if this were the case, the inclusion of primary complex TB in a composite or multiple efficacy endpoint would artificially decrease observed vaccine efficacy. However, this hypothesis is not supported by some data from historical BCG vaccine trials. For example, in a BCG vaccine trial among Native American children in the pre-chemotherapy era, Aronson et al showed the same protective efficacy against isolated intrathoracic lymphadenopathy as for uncontained pulmonary disease, disseminated disease, and death due to TB (29). Yet, in this trial, 87% of children with isolated intrathoracic lymphadenopathy at the time of first observation did not progress to more severe forms of disease, even without effective anti-tuberculous chemotherapy.

The clinical relevance of primary complex TB is unclear and this early, mild, and potentially self-limiting disease phenotype has occasionally been classified as infection, rather than disease (6, 9, 28). Tobias Gedde-Dahl has noted this contention, but took the position that TB disease is characterized by ‘a biologically active process demonstrable either clinically or radiologically’, and that the objective radiological evidence of TB disease includes a radiological demonstration of the primary complex (30). However, although it is accepted that infants will develop disease early after infection (progressive primary infection), the clinical distinction between primary infection and relevant disease is not always clear in infants and children. The concept of relevant TB disease would also vary by setting and age. For example, the primary infection in childhood might not be treated with antituberculous drugs in some high prevalence, low resource settings, in which the majority of children successfully contain infection without treatment. However, recent primary infection among children younger than two years of age would be considered a relevant disease, even in low resource settings, given the risk of disease progression in the absence of treatment (2). It is thought that age and immunodeficiency are the two most important factors determining whether primary TB progresses, or remains contained. For example, in young and immune-compromised children, poor cell-mediated immunity is thought to allow bacilli to proliferate with progressive parenchymal damage and potential dissemination.

The decision on whether or not to include primary complex TB within composite or multiple endpoints for infant TB vaccine trials will be crucial, given the much lower incidence of advanced and disseminated TB disease in modern research settings. By contrast, early clinical trials of BCG vaccination among infants were conducted in the era prior to effective chemotherapy and prophylaxis against TB disease (31, 32).
It follows that TB disease endpoints were usually characterized by the most severe phenotype observed during the natural history of the disease, despite the best medical care available at that time. Thus, the cases of TB disease observed in these trials were often characterized by advanced pulmonary and disseminated disease and death. However, not all the historical BCG vaccine trials have focused exclusively on disseminated and advanced disease, for example, Aronson et al included, as TB cases, deaths due to TB, extrapulmonary TB (including TBM), moderately and far-advanced pulmonary TB, as well as minimal pulmonary TB, pleural effusion, and enlarged hilar glands, both with and without parenchymal involvement (29). Primary complex TB comprised approximately one sixth of all cases of disease. Furthermore, in this study, infant BCG vaccination appeared equally efficacious in preventing primary complex TB without parenchymal involvement (contained disease), as it was in preventing uncontained and disseminated TB disease. This distinction is important, since it has been proposed that the incidence of transient primary complex TB, representing the desirable immune containment of \(MTB\), might actually be increased by an effective TB vaccine (19). The data from Aronson et al suggest that, at least for BCG, this is not the case (29). The next challenge for childhood TB vaccine trials lies in determining, \textit{a priori}, which individual cases of primary complex TB would resolve spontaneously, and which cases would progress to uncontained pulmonary or disseminated TB disease. Since such children would almost always receive anti-tuberculous therapy, which would halt any further disease progression, this differentiation is not possible with the diagnostic tools that are currently available. Wiseman et al have recently proposed an objective classification of severity of childhood TB disease, based on clinical, radiological, histological, and bacteriological data, which may be used to standardize endpoint definitions for paediatric TB vaccine trials (33). The authors propose that TB disease in children is classified not only by anatomical location, but also by the extent of disease at the site of primary pathology (contained or uncontained); and by the presence or absence of complications. Using this system, the TB disease that is disseminated, or uncontained, or complicated (e.g. airway compression), would be classified as severe. By contrast, TB disease that is contained and without complications, such as primary complex TB in the lung, would be classified as non-severe. This classification has the potential to standardize the interpretation of TB case definitions across studies, in that it is independent of symptoms and includes mild forms of TB disease, including phenotypes that might previously have been classified as ‘infection’.
DIAGNOSTIC CHALLENGES

Diagnosis of childhood TB in the setting of clinical trials of new TB vaccines will present two distinct challenges: firstly, the definitive microbiological or molecular identification of *MTB* as the aetiological agent; and secondly, the careful description of the clinical and/or radiological criteria for the clinical syndromic definition of TB disease (34, 35). It does not appear that surrogate measures of TB infection, eg interferon-gamma release assays (IGRAs), will substitute for culture or molecular confirmation of *MTB* in the diagnosis of TB disease (36, 37). It was initially hoped that IGRAs would provide a more sensitive and specific test for TB infection than the TST. The TST may be false negative due to immunosuppression, malnutrition, or poor technique; and false positive due to prior BCG vaccination or non-tuberculous mycobacterial exposure. However, there is insufficient evidence to indicate that IGRAs should be used in preference to the TST to detect TB infection, especially in children younger than two years of age (36, 37). Furthermore, IGRAs have shown relatively poor diagnostic performance for the detection of TB disease in children, particularly in high burden countries (36). However, the microbiological confirmation of TB disease has always been difficult. Young children usually do not produce sputum and have pauci-bacillary disease, with the result that childhood TB is usually sputum smear negative (34, 35). Microbiological confirmation rates are consistently lower in children than adults. Therefore, diagnosis has traditionally hinged on clinical history, including history of contact with infectious adult cases; chest radiography; and positive TST. However, this approach is littered with challenges. TST is often negative in culture-proven TB, due to immune suppression (38). More than half of younger children and infants with TB may be asymptomatic and need CXR to confirm the diagnosis (39). Due to this apparent diagnostic difficulty, clinicians in high burden countries have a low threshold for diagnosis and treatment of TB, yet many TB cases in Africa are only diagnosed at autopsy.

It has been generally accepted that *MTB* is cultured in fewer than 50% of child TB suspects, but this proportion may actually be less than 25%, given recent findings from South Africa (2.3%; 11.9%; 16%; 22.4%; and 25%) (16, 24, 40, 41); Rwanda (5%) (42), and Peru (10%) (43). Several techniques to maximize the diagnostic yield from the mycobacterial culture of respiratory sample have been used in children, with variable success. Zar *et al* have shown that the yield from a single induced sputum is equivalent to that from three consecutive gastric lavages in hospitalized children (overall yield 25%) (40). However, the yield from induced sputum and gastric lavage was equivalent in a community-based study from the same region (overall yield 10%) (44). Other sample techniques that have shown some promise,
but that have not gained widespread usage include nasopharyngeal aspiration, the ‘string’ test, and stool collection (35). For example, in a Peruvian study by Oberhelman et al., 10% of symptomatic child TB suspects were MTB culture positive by either gastric aspirate, nasopharyngeal aspirate, or stool sample (43). The addition of a second gastric aspirate resulted in 37% increased yield, compared to a single gastric aspirate. In this study, the diagnostic yield, as a percentage of all culture-confirmed cases, was clearly superior for gastric aspiration, compared to nasopharyngeal aspiration (55%) and stool collection (18%). However, heminested IS6110 PCR was judged insufficiently sensitive or specific in this study. New rapid molecular diagnostic techniques have delivered swifter sample processing, coupled with drug sensitivity testing, but may lack sensitivity in pauci-bacillary paediatric TB disease. Xpert MTB/RIF (Cepheid, Sunnyvale, USA) is an integrated sample processing and nucleic acid amplification test for the detection of M. tuberculosis and resistance to rifampicin that offers the advantage of high sensitivity and very rapid turnaround in adult studies. A single MTB/RIF test has 92% sensitivity for all culture-positive TB diseases in adults, although more modest 73% sensitivity is recorded among patients with sputum smear-negative, culture-positive disease (45). However, although rapid turnaround and the ability to detect mono-resistance is a major advance in the era of MDR and XDR TB, recent work has not fulfilled the promise of a highly sensitive diagnostic gold standard for childhood TB. Almost one quarter of hospitalized children with culture-confirmed TB in a South African study were Xpert MTB/RIF negative (sensitivity 74%), and this proportion is even worse for smear-negative culture-confirmed TB (sensitivity 58%) (46). Furthermore, it appears that two Xpert MTB/RIF samples would be needed for optimum diagnostic yield, since the sensitivity of a single Xpert MTB/RIF test for smear-negative TB was only 33%.

Given the limited sensitivity of culture and molecular techniques, efforts have been made to increase the diagnostic accuracy of clinical and radiological approaches to childhood TB. For example, Marais et al. have studied the use of symptom-directed diagnosis in a high TB-burden urban South African community (2003 – 2005) among 214 of 1024 child TB suspects <10 years of age (21%) who were diagnosed with TB (24). Among children ≥3 years of age, a composite endpoint including persistent unremitting cough and documented growth failure has shown 82% sensitivity and 90% specificity for confirmed or probable TB. However, these two criteria show only 68% sensitivity and 80% specificity among children younger than three years. This finding underscores the fact that TB disease presents more acutely in younger children, with a smaller window of opportunity for symptom-based diagnosis. This problem is compounded by the greater risk of progression to
disseminated military and meningitic disease in the relative absence of symptoms in very young children (6). Chest radiography may be pivotal in the diagnosis of individual cases of pulmonary TB, particularly those that present later in the course of the disease, with classical radiological features. However, the diagnostic accuracy of chest radiography for intrathoracic lymphadenopathy, the cardinal radiographic feature of pulmonary TB, is not optimal even in hospitalized children. Swingler et al. showed that the sensitivity and specificity of chest radiography for CT-confirmed intrathoracic lymph nodes are only 67% and 59%, respectively (47, 48). Notably, a lateral view does not add to diagnostic accuracy; and chance-adjusted agreement between reviewers is poor (30%). Attempts have been made to improve the reliability and accuracy of clinical childhood TB diagnosis by combining symptoms, signs, chest radiography, and microbiologic variables in data-driven approaches. These have included several numerical scores, diagnostic algorithms, and other systematic approaches. Unfortunately, none have been validated and these scores show highly variable performance when compared in a single population (49). For example, the TB case frequency among 1,445 South African children younger than two years of age varied between 7–89%, depending on which of the nine structured approaches for screening and diagnosis was used to define TB (50). The structured approaches that use the most stringent criteria showed only slight agreement (kappa 0.18), implying that different subpopulations or phenotypes of TB are being identified. The challenge of making a TB diagnosis is increased several-fold among HIV-infected children (13). Symptoms of growth failure, weight loss, and persistent cough may be due to HIV infection or HIV co-morbidities, the TST is less sensitive in HIV-infected children, and it may be difficult to distinguish radiographic features of TB from HIV–related bacterial pneumonia, lymphocytic interstitial pneumonitis, or bronchiectasis. However, the diagnostic yield of respiratory sample collection methods seems to be similar between hospitalized, HIV-infected and uninfected children (40).

The main difficulty for infant TB vaccine trials lies in the distinction between diagnostic accuracy and disease severity in designing composite or multiple endpoint criteria. Diagnostic criteria such as the culture of MTB might be highly specific, but lack the ability to assess disease severity. Similarly, the collection of symptom variables allows the assessment of the degree of clinical impairment, but lacks specificity for TB disease. These dilemmas were highlighted in the recent Consensus Statement on diagnostic endpoints for infant TB vaccine trials, which highlighted concerns over the significance of MTB culture in children without supporting clinical and radiological features of disease (28). However, the classification of childhood TB disease severity that has recently been proposed, which classifies TB disease
as non-severe or severe, depending on the anatomical site, extent (contained or uncontained), complications, and dissemination, may have considerable utility for TB vaccine trials (33). For example, this classification would categorize a contained primary focus with uncomplicated enlargement of draining lymph nodes as non-severe TB disease, regardless of whether the regional lymphadenopathy was pulmonary, abdominal, or cervical. Notably, the proposed classification does not include symptoms in the assessment of disease severity. The classification of TB disease severity would allow a two-stage approach to the definition of vaccine trial endpoints, in which clinical, radiological, and microbiological diagnostic criteria are used to determine and define the presence or absence of TB disease; and thereafter, the proposed pathological classification might be used to stratify severity among those children diagnosed with TB.

REFERENCES


