Global epidemiology of childhood TB: book chapter

pre-publication draft

Prepared by:
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Questions for discussion

1. Are there suggestions for modifications to the statistical approach for estimation of childhood TB incidence that would improve the appeal of this approach?

2. Are there suggestions for modifications to the statistical approach for estimation of childhood TB mortality that would improve the appeal of this approach?

3. Are there any suggestions for expansion of the statistical approach that will allow disaggregation of incidence and mortality estimates by HIV status?
Global Epidemiology of Paediatric Tuberculosis

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1. Introduction

Tuberculosis (TB) is likely to have affected humans for most of their history (Holloway et al. 2011; Comas et al. 2013) and remains a major cause of morbidity and mortality worldwide despite the discovery of effective and affordable chemotherapy more than 60 years ago. In 2013, there were an estimated 9 million incident cases of TB and 1.5 million deaths from the disease (1.1 million among HIV-negative and 0.4 million among HIV-positive TB) (WHO 2014a). TB and the human immunodeficiency virus (HIV) are the top causes of death from an infectious agent (Lozano et al. 2012; Ortblad et al. 2013). TB is a leading killer among people in the most economically-productive age groups and those living with HIV (Lopez et al. 2006).

Every year, WHO publishes estimates of TB incidence, prevalence and mortality at global, regional and country levels, along with an analysis of progress towards achievement of global international targets for TB (MDG6c target of halting and reversing TB incidence and other international targets of halving prevalence and mortality by 50% compared with 1990 levels) (WHO 2014a). Increased global attention on maternal and child health recently has created a demand for, and interest in, TB disease burden estimates disaggregated by age and sex. TB disease burden estimates for children (throughout this chapter a child is defined as aged less than 15 years) were published for the first time by WHO in 2012 (WHO 2012a) and showed that, every year, at least half a million children less than 15 years are affected by the disease.

Over-burdened health systems traditionally attributed low priority to the largely non-infectious TB cases among children. As a result, currently much is left to be desired in terms of availability of child-appropriate diagnostic and treatment tools, as well as robust and nationally-representative surveillance and survey data. As a direct result of the global focus on maternal and child health, clearly articulated actions have recently been defined for all stakeholders involved to address historical shortcomings to childhood TB, including: a) strengthening surveillance through better recording and reporting and engagement with the private sector, especially paediatricians; b) incorporating TB screening in existing maternal and child health services, especially in TB endemic settings; c) addressing knowledge and research gaps in epidemiology, basic and operational research, and the development of new tools – such as diagnostics, drugs, vaccines (WHO 2013b).
This chapter describes our current understanding of the global burden of paediatric TB disease; the reasons why it remains difficult to estimate disease burden in children; the data sources available to inform disease burden estimation in children; the progress made the last few years through the collaboration of key partners with the development of complementary methods to produce burden estimates; and the next steps planned to improve those estimates.

2. TB epidemiology

TB is contagious and airborne (Riley 1983). Susceptible individuals acquire *M. tuberculosis* infection through inhalation of bacteria contained in droplet nuclei dispersed in the environment by individuals with tuberculosis of the lungs or the airways. When coughing, sneezing, or speaking, such individuals aerosolise droplet nuclei that are then passed to others. Other routes of transmission are very uncommon and of no epidemiologic significance. The probability of contact with a person who has an infectious form of TB, the intimacy and duration of that contact, the degree of infectiousness of the case, the virulence of the bacterial strain, and the shared environment in which the contact takes place are all important determinants of the likelihood of transmission. About one third of the world’s population is estimated to be latently infected with *M. tuberculosis* (WHO 2013a). Of those infected, only a small proportion (less than 10%) will ultimately become sick with TB (Vynnycky E et al. 2000; Borgdorff et al. 2011) but very young children, people with weakened immune systems, people living with HIV, patients with renal insufficiency, silicosis, diabetes and other morbidities, have a much greater risk of falling ill from TB. We know from historical data that if left untreated, smear-positive, infectious tuberculosis among HIV-uninfected individuals has a 10-year case fatality variously reported between 53% and 86%, with a weighted mean of 70% (Tiemersma et al. 2011), compared with about 3% of HIV-uninfected treated tuberculosis patients (Straetemans et al. 2011). TB is a disease of poverty that thrives where social and economic determinants of ill health prevail. It affects mostly young adults in their most productive years living in the developing world (WHO 2013a).

3. Global monitoring of the burden of paediatric TB

3.1 Existing challenges to estimating disease burden in children

There are important challenges that currently prevent the accurate measurement of the number of TB cases and deaths among children. First of all there is no point-of-care, easy-to-use and accurate diagnostic test for confirming TB disease in children. Most children have paucibacillary pulmonary TB that is harder to diagnose with
available laboratory tests (such as sputum smear microscopy and culture). Children are often not able to expectorate sputum, which means that obtaining a specimen requires induced sputum techniques such as gastric lavage, nebulization, or bronchoalveolar lavage. These procedures in turn require a hospital setting, overnight hospitalization, an appropriate infection control environment and trained personnel. Therefore, usually diagnosis is usually made using a combination of clinical criteria and a non-specific test for tuberculous infection such as tuberculin skin test or interferon-gamma release assay (IGRA). There are several diagnostic algorithms that have been proposed, but none has been universally applied, thus making comparisons over time and space difficult. Furthermore, the definitive diagnosis of extrapulmonary TB requires specialised services that are usually available only in referral tertiary hospitals, and thus often not accessible to those most in need. Besides the known diagnostic challenges, children diagnosed with TB are not always reported to national surveillance systems because of the lack of linkages among individual paediatricians and paediatric hospitals and national TB programmes, and data from national surveys including children are limited. Many countries lack vital registration (VR) systems in which deaths from TB are reported and disaggregated by age.

3.2 TB incidence

TB incidence has never been measured at national level because this would require long-term studies among large cohorts of people (hundreds of thousands) at high cost and with challenging logistics. However, health information systems in many countries are not yet capable to provide a direct measure of TB incidence as an unknown number of cases are either treated but not notified or go undiagnosed. The major reasons why cases are missed from official notification data include laboratory errors (Botha et al. 2008), lack of notification of cases by public (Dye et al. 1999) and private providers (Uplekar et al. 2001), failure of people accessing health services to be identified as potential TB cases (Meintjes et al. 2008) and lack of access to health services (Veron et al. 2004). The best approach to estimating TB incidence is from routine surveillance systems in which case reports disaggregated by age and sex are more or less complete, such that notifications can be considered a close proxy of incidence. This is possible in settings with universal health care coverage (Moreno-Serra and Smith 2012; O’Neill et al. 2013), and where operational research has been used to quantify the small fraction of cases that are treated but not notified to surveillance systems (Van Hest et al. 2008). Recent efforts to improve our understanding of the gap between TB surveillance systems and the true incidence level are very promising and include the design and implementation of nationwide inventory surveys to measure under-reporting of childhood TB,
primarily from the private but also the public sector, in high priority countries in Asia (WHO 2012b; WHO 2014b).

3.3 TB mortality
TB mortality among HIV-negative people can be directly measured using age-disaggregated data from national vital registration (VR) systems, provided that these systems have high coverage and causes of death are accurately coded according to the latest revision of the *International classification of diseases* (ICD-10) (E. L. Korenromp 2009). Sample VR systems covering representative areas of the country (e.g. China) provide an interim solution. Direct measurements of TB mortality from 130 countries were used in 2014 (WHO 2014a). The parts of the world where there are major gaps in the availability of VR data are the African Region and parts of the South-East Asia Region; in the latter, Indonesia is currently building a sample VR system.

TB mortality among HIV-positive children is hard to measure directly even when national VR systems with standard coding of causes of death are in place because deaths among HIV-positive people are coded as HIV deaths and contributory causes (such as TB) are generally not reliably recorded. This will need to be corrected in future iterations of ICD to permit a proper assessment of TB mortality. In the interim, indirect estimation of TB mortality among HIV-positive children is the only option, using data on contributory causes of AIDS death from well-monitored cohorts of HIV-positive people on care and autopsy studies.

3.4 TB prevalence
There is currently no global data source available that monitors the prevalence of TB disease in children. Bacteriologically-confirmed TB prevalence among adults (aged more than or equal to 15 years) is measured in nationwide population-based surveys in countries with a high burden of TB (Glaziou et al. 2008; WHO 2011a). Since 2002, 22 countries have successfully measured the prevalence of TB disease through such surveys, including 10 in Africa (Hong Y.P. 1998; Tupasi et al. 1999; Dye et al. 2000; Soemantri et al. 2007; WHO 2014a), while an additional 10 countries (3 in Africa) have planned to implement a survey by 2015.

Review of historical data from national surveys of pulmonary TB targeting children found that, while the group including some of or the entire 0-14 age category made up about 20-30% of the total sample size of the survey, it only included about 1-4% of the total number of smear-positive and 2-7% of bacteriologically-confirmed TB cases found by the survey (*Table 1*). Furthermore, in the context of the current design of national prevalence surveys to estimate pulmonary TB:
The inclusion of children in a survey would not lead to a precise estimate of TB prevalence among children, since only a few bacteriologically-confirmed cases would be found. Even existing surveys are not able to provide precise estimates for different age groups.

There are ethical considerations associated with mass screening of all children, most of whom are healthy. While evidence exists that chest X-ray screening is safe for adults, similar evidence does not exist for children. Furthermore, there is no simple and reliable tool that could be used to restrict the number of children screened by X-ray.

Among adults, “over-reading” of X-rays is encouraged to minimize the number of cases that are missed. Among children, use of tests for tuberculous infection and over-reading of X-rays would lead to unnecessary efforts to obtain specimens, which among young children requires invasive and uncomfortable gastric aspiration.

Referral hospitals are needed for the follow-up and diagnostic confirmation of TB in children. These are often not available in the rural areas that account for a large share of the clusters included in national prevalence surveys.

Inclusion of children would approximately double the sample size and associated costs. The additional logistical complications of including children could also jeopardise the survey as a whole.

### TABLE 1. Evidence from past national TB prevalence surveys that included children: numbers and rates per 100,000 of smear-positive and bacteriologically-confirmed TB cases among the age group including some of or the entire 0-14 childhood age category

<table>
<thead>
<tr>
<th>NATIONAL SURVEYS</th>
<th>Age group including children (column B)</th>
<th>Total number of survey participants – all ages (%)</th>
<th>Number of S+ cases N (%$^5$)</th>
<th>S+ rate per 100,000</th>
<th>Number of B+ cases N (%$^5$)</th>
<th>B+ rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>China 1990$^a$</td>
<td>0-14</td>
<td>401,997 (28)</td>
<td>30 (2)</td>
<td>7</td>
<td>51 (2)</td>
<td>13</td>
</tr>
<tr>
<td>China 2000$^{2,b}$</td>
<td>0-14</td>
<td>89,295 (24)</td>
<td>6 (1)</td>
<td>7</td>
<td>11 (2)</td>
<td>12</td>
</tr>
<tr>
<td>Cambodia 2002$^{2,c}$</td>
<td>10-14</td>
<td>4,591 (21)</td>
<td>3 (4)</td>
<td>65</td>
<td>4 (1)</td>
<td>87</td>
</tr>
<tr>
<td>Philippines 1997$^d$</td>
<td>10-19</td>
<td>4,989 (31)</td>
<td>6 (9)</td>
<td>120</td>
<td>18 (10)</td>
<td>361</td>
</tr>
<tr>
<td>Philippines 2007$^e$</td>
<td>10-19</td>
<td>6,728 (29)</td>
<td>1 (2)</td>
<td>15</td>
<td>11 (7)</td>
<td>163</td>
</tr>
<tr>
<td>Republic of Korea 1990$^f$</td>
<td>5-19</td>
<td>16,468 (34)</td>
<td>2 (3)</td>
<td>12</td>
<td>5 (4)</td>
<td>30</td>
</tr>
<tr>
<td>Republic of Korea 1995$^g$</td>
<td>5-19</td>
<td>19,005 (29)</td>
<td>1 (2)</td>
<td>5</td>
<td>2 (1)</td>
<td>11</td>
</tr>
</tbody>
</table>
Taking all of the above under consideration, as well as the performance of existing screening and diagnosis tools, the inclusion of children in the current design of national prevalence surveys that estimate pulmonary TB is not currently recommended, but instead attention is focused on strengthening surveillance systems so they can provide reliable and complete data on new TB cases and TB deaths among children. Those adult TB cases that are found as part of prevalence surveys of pulmonary TB provide an opportunity for household contact investigation and identification of children with active TB disease and/or those less than 5 years eligible for isoniazid preventive treatment of latent tuberculous infection.

### 3.5 Drug-resistant TB

Estimates of the incidence and mortality of MDR-TB are derived from periodic surveys or from routine drug-susceptibility testing (DST) if the coverage of patient testing is sufficiently representative (WHO 2014a). The global surveillance of resistance to the two most important first-line anti-TB drugs - isoniazid and rifampicin – has been coordinated by the World Health Organization (WHO) since 1994 (Pablos-Méndez A et al. 1997). Due to the lack of consistently reported age-disaggregated results from these surveys, WHO does not currently publish global estimates of drug resistance among children. Research groups have attempted to address this gap, estimating incidence of multidrug-resistant TB among children for 2013 at 32,000 (95% confidence interval 26,000 – 39,000) (Jenkins et al. 2014).

### 3.6 Burden of tuberculous infection

Nationally representative tuberculin skin test surveys were traditionally used to measure the prevalence of tuberculous infection and determine the annual risk of infection (which under a number of assumptions was also translated into an
estimate of incidence of TB disease). However, well-documented shortcomings with the conduct, analysis and interpretation of such data, as well as evidence that contradicted the underlying assumptions, discontinued the conduct of such surveys (Dye 2008; van Leth et al. 2008; WHO 2009). In the absence of an accurate diagnostic test for infection and due to the lack of recent nationally representative data WHO does not currently publish global estimates of the burden of tuberculous infection. However, a mathematical modelling exercise has attempted to address this gap and estimated that in 2010 there were about 53,000,000 (95% confidence interval 41,000,000 – 69,000,000) children with latent tuberculous infection in the world (Dodd et al. 2014).

4. Incidence

4.1 Age-disaggregated TB case notifications
Routine recording and reporting of the numbers of TB cases diagnosed and treated by NTPs and monitoring of treatment outcomes was one of the five components of the global TB strategy (DOTS) launched by WHO in the mid-1990s (WHO 1994) and remained a core element of its successors, the Stop TB Strategy (Raviglione et al. 2006) and End TB Strategy (WHO 2014c). With the standard definitions of cases and treatment outcomes recommended by WHO and associated recording and reporting framework as a foundation, global monitoring of trends in case notifications and treatment outcomes has been possible since 1995.

Age and sex disaggregation of smear-positive TB case notifications has been requested from countries since the establishment of the data collection system in 1995, but with few countries actually reporting these data to WHO. In 2006, the data collection system was revised to additionally monitor age disaggregated notifications for smear-negative and extra-pulmonary TB. The revision also included a further disaggregation of the 0–14 age group category to differentiate the very young (0–4) from the older children (5–14). While reporting of age disaggregated data was limited in the early years of the data collection system, coverage kept improving until for 2012 case notifications it reached 99%, 83% and 83% out of total smear-positive, smear-negative and extra-pulmonary TB case notifications notified respectively that were age and sex disaggregated. Finally in 2013, another revision of the recording and reporting system was necessary to allow for the capture of cases diagnosed using WHO-approved rapid diagnostic tests (such as Xpert MTB/RIF) (WHO 2013c). This current revision requests the reporting of all new and relapse case notifications by age and sex (but not separately by case type). The countries that reported age-disaggregated data in 2013 can be seen in Figure 1.
While some nationwide surveys exist that have quantified the amount of under-reporting of cases diagnosed in the health sector outside the network of the national TB programmes (Bassili A et al. 2010; Van Hest R et al. 2007; Van Hest R et al. 2008), none have produced precise enough age-disaggregated results. Small-scale, convenient-sampled studies in some settings indicate that under-reporting of childhood TB is very high (Lestari et al. 2011) but extrapolation to nationally representative, regional and global settings is not yet possible. This shortcoming is currently being addressed through the plans for implementation of national scale surveys in high priority countries in Asia to measure under-reporting of TB in children (WHO 2014b).

4.2 Complementary methods of estimation

The first estimation approach to quantify TB incidence in children, published by WHO in 2012, was based on TB case notifications corrected for the estimated gap from true incidence due to under-reporting and under-diagnosis with well-described strengths and limitations (WHO 2012a). Since then, alternative approaches to indirectly estimate incidence and improve our understanding of disease burden in children, were commissioned to research groups that were presented and reviewed during a global consultation in 2013 on methods to estimate childhood TB burden. By early 2014, both these approaches (Dodd et al. 2014; Jenkins et al. 2014) including an additional independent approach (Murray
CJL et al. 2014) were published. Comparing results between approaches (Figure 2) shows large discordance that ultimately highlights the weaknesses of the underlying data and the urgent need for strengthening surveillance and improving the direct measurement of TB disease in children.

**FIGURE 2.** Comparison of different indirect estimation attempts to get to the number of incident childhood TB cases for 2013 (vertical bars represent 95% uncertainty bounds)

To estimate TB incidence in children for 2013, an ensemble statistical approach was used to combine results from two of the independent methods presented in Figure 2 (WHO 2014a). The third method is currently being further refined with additional data review efforts to inform parameters critical to the estimation process (Sismanidis C et al. 2014). The fourth method is currently excluded due to the lack of information on the uncertainty of the estimate (Murray CJL et al. 2014).

Childhood TB incidence in 2013 is estimated to be 550,000 (95% uncertainty bounds 470,000–640,000), equivalent to about 6% of the total number of 9 million incident (all ages) cases (WHO 2014a).

**4.3 Next steps to improve estimation and ongoing analytical work**

The key future efforts that will mostly contribute to the improvement of the estimation of TB incidence among children are, first the promotion of case-based electronic recording and reporting systems that will facilitate the compilation and analysis of age-disaggregated data at national and sub-national levels; second, the
implementation of nationwide inventory surveys in high priority countries to measure under-reporting of childhood TB; third, intensified household contact-tracing activities of index adult TB cases, as well as the integration of TB activities in maternal, newborn and child health services, to identify childhood cases that otherwise go undiagnosed.

Finally, the currently ongoing analytical work, coordinated by WHO and conducted by collaborating research groups, aims to produce robust estimates of incidence for regions and countries, as well as disaggregate global TB incidence by HIV-status and multi-drug resistance status, by the end of 2016.

5. Mortality
Mortality data reported to WHO from VR systems that were disaggregated by age were available for 111 countries for 2013 (Figure 3). These data were used to calculate TB death rates per 100 000 population for children and adults, after adjustment for incomplete coverage and ill-defined causes, and impute data for countries without VR (WHO, 2014a). The total number of deaths from TB among HIV-negative children was estimated to be 80 000 (range, 64 000–97 000), equivalent to about 7% of the total number of 1 100 000 TB deaths among HIV-negative people in 2013 (WHO 2014a). An alternative independent approach produced a lower estimate of about 60 000 deaths (Murray CJL et al. 2014).

FIGURE 3. Countries (in green) for which TB mortality is estimated using age-disaggregated measurements from vital registration systems (n=111)
To improve estimates of TB mortality among children, the next steps are: first, to collect age-specific data from sample vital registration systems and mortality surveys in high-burden countries including China, India and Indonesia. Second, to advocate for further development of, and continued investment in, VR systems.

Currently ongoing analytical work, aims to produce robust estimates of TB mortality for regions and countries, as well as estimate global TB mortality among HIV-positive children by the end of 2016.

6. Epidemiological strategies to decrease TB burden among children

WHO currently recommends the active screening for TB of all children, especially those living with HIV or in the households of adults diagnosed with active TB disease (WHO 2011b; WHO 2012c; WHO 2014d). The main purposes of contact screening and management are: first, early identification of all contacts of an index TB case with undiagnosed TB disease to improve treatment outcomes and prevent further transmission of infection and second, to identify all contacts recently infected who do not have active TB disease and are eligible for provision of chemotherapy to prevent the onset of disease. Among children in close contact with a TB case those eligible for chemoprophylaxis are all children under the age of 5 and all HIV-positive children.

7. Conclusions

The lack of child-appropriate tools to confirm diagnosis of TB disease, standard case-definitions, and the complete recording and reporting of children that are diagnosed with TB disease and put on treatment continue to pose significant shortcomings to the robust estimation of burden due to TB in children. Despite that, remarkable progress has been made since the first official set of WHO estimates for childhood TB was published in 2012. In less than three years since then global interest to improve these estimates has been ignited, with countries around the world improving their recording and reporting practises for age disaggregated data, multiple collaborating research groups working with WHO to improve our understanding of TB disease burden in children, and for the first time ever a number of high priority countries in Asia are planning to implement national scale studies to measure the level of TB under-reporting in children.
WHO estimates that in 2013 there were 550,000 (95% uncertainty bounds 470,000–640,000) new childhood TB cases and 80,000 deaths due to TB (range, 64,000–97,000) among children that were HIV-negative. Independent research groups estimate there are 32,000 (95% confidence interval 26,000 – 39,000) children with MDR-TB and an astounding 53,000,000 (95% confidence interval 41,000,000 – 69,000,000) children with latent tuberculous infection, the future pool of TB cases of tomorrow. The sheer magnitude of tuberculous infection and tuberculosis morbidity and mortality places childhood TB high as a global public health priority and demands our continued attention and commitment.
8. References


http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf?ua=1