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The burden of multidrug-resistant tuberculosis in children

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Abstract

Background—Childhood tuberculosis (TB) has been historically neglected, although in recent years there has been increased focus on this problem. In particular, there have been several efforts to estimate the pediatric multidrug-resistant TB (MDR-TB) burden.

Methods—We review current estimates of the global incidence of pediatric MDR-TB disease. We then combine pediatric MDR-TB treatment data from the World Health Organization and recently published case fatality ratio estimates for children with TB to produce mortality estimates for children with MDR-TB. Finally, we combine treatment data and estimates of household size and disease risk to estimate how many children could be treated for presumptive MDR-TB by carrying out household contact investigations around adult MDR-TB patients.

Results—Between 25,000 and 32,000 children develop MDR-TB disease annually, accounting for around 3% of all pediatric TB cases. Only 3-4% of these children likely receive MDR-TB treatment. We estimate that around 22% of children developing MDR-TB disease will die. We estimate that carrying out household contact investigations around adult MDR-TB patients could find twelve times as many pediatric MDR-TB cases as are currently being identified.

Discussion—The diagnosis and treatment of children with MDR-TB needs to be prioritized by TB programs.

Introduction

Children with tuberculosis (TB) have historically been a neglected population. Diagnosing multidrug-resistant TB (MDR-TB; a strain of TB that is resistant to at least isoniazid and rifampin) is especially problematic in children, from whom it is difficult to isolate a bacteriologic specimen that can be used to directly detect drug resistance[1]. Estimates of the number of children who develop MDR-TB each year have been published, but knowledge is lacking regarding whether they are diagnosed or treated, and whether they survive. In this article, we provide an extended introduction that reviews the current knowledge of the MDR-TB burden in children. We then seek to add to existing knowledge by estimating MDR-TB-associated mortality in children and the potential impact of contact investigations on closing the treatment gap.

The first estimate of the global number of children that develop MDR-TB disease annually was published in 2014[2]. This paper, by Jenkins et al., reported a global estimate of 32,000

(95% Confidence Interval (CI): 26,000, 39,000) annual incident pediatric MDR-TB cases. To produce this number, the authors first generated new country-level estimates of incident pediatric TB cases. The authors used the number of pediatric smear-positive pulmonary TB cases reported by each country to the World Health Organization (WHO)[3] and scaled these up using estimates of the proportion of all pediatric TB cases that is expected to be smear positive[4]. To determine how many of these children had MDR-TB, the authors then carried out a systematic review of the literature from which they identified 31 studies that reported cohorts comprising both children and adults with incident TB, all of whom had been evaluated for MDR-TB. They then quantified the relationship between the proportion of children who had MDR-TB and the proportion of adults who had MDR-TB by fitting a regression to the data. They found that the proportion of pediatric TB patients that have MDR-TB is reflective of the proportion of new adult TB patients that have MDR-TB in the same setting, a finding that was later confirmed by WHO survey and surveillance data[5]. Using this relationship, Jenkins et al. used WHO 2010 estimates of the proportion of new adult TB cases that were MDR-TB[6] to estimate the proportion of pediatric TB that is MDR-TB for every country in the world, and applied these proportions to their country-specific pediatric TB estimates.

In 2016, Dodd et al. published an estimate of 25,000 (inter quartile range (IQR): 16,000, 37,000) annual incident pediatric MDR-TB cases using an independent method[7]. This method involved using a mathematical model of transmission, accounting for factors such as HIV co-infection and BCG vaccination, that had been used previously to estimate global pediatric TB incidence[8]. Similar to Jenkins et al., Dodd et al. assumed that the risk of MDR-TB among pediatric TB patients was reflective of the risk of MDR-TB among new adult TB patients; they obtained data on adult patients from drug resistance surveys reported during 1988–2014. Dodd et al. then combined these risks with their own pediatric TB incidence estimates. The main reason for the difference between the estimates of Jenkins et al. and Dodd et al. is in the underlying assumption of pediatric TB incidence: 1 million in Jenkins et al.[2] and 850,000 in Dodd et al.[7]. Both papers suggest that MDR-TB cases account for approximately 3% of the pediatric TB burden.

Of the tens of thousands of children estimated to develop MDR-TB each year, a small fraction is diagnosed. Although exact figures have not been published, in 2015, fewer than 1,000 children with MDR-TB were reported to WHO from all member states (personal communication, Global TB Programme, WHO). This corresponds to only 3–4% of the children estimated to have developed MDR-TB. If MDR-TB is not diagnosed, then children will not receive appropriate treatment, defined as treatment that is likely to be effective against the drug resistance profile of the TB strain of the patient.

What are the consequences of this large gap between the number of children who fall sick with MDR-TB and the number who receive appropriate treatment? And how can this gap be closed? To start to address these questions, we estimate the number and proportion of children who die from MDR-TB each year. Furthermore, we estimate the number of additional children who could be identified as having probable MDR-TB disease and infection and treated accordingly if household contact investigations were performed for all adult MDR-TB patients.

Methods

Mortality in children with MDR-TB

We derived crude estimates of the mortality burden due to pediatric MDR-TB by combining pediatric MDR-TB incidence estimates, estimated numbers of treated versus untreated children, and case fatality ratios for treated and untreated children. Annual MDR-TB incidence estimates of both 32,000 and 25,000 are considered based on the two estimates that have been published to date[2,7]. We conservatively assumed that 1,000 children receive appropriate treatment. A systematic review and meta-analysis of outcomes among children treated for MDR-TB estimated that 5.9% (95% CI: 1.3%, 10.5%) of children treated for MDR-TB died[9]. A recent literature review of case fatality ratios in children with TB estimated that 22% (95% CI: 18%, 26%) of children (<15 years) with TB died in the era prior to the development of anti-TB treatment[10]. Thus, assuming that the risk of death without TB treatment does not vary by drug resistance profile, we used a case fatality ratio of 22% for children with MDR-TB who do not receive MDR-TB treatment, although we acknowledge that this may overestimate mortality since some children receive treatment for drug-susceptible TB, potentially exposing them to one or two effective antibiotics.

To estimate the number of children who die from MDR-TB annually, we applied the case fatality ratio for treated children (5.9%) to the estimated 1,000 children who receive MDR-TB treatment. We then applied the case fatality ratio for untreated children (22%) to the remainder of the children who are estimated to develop MDR-TB but who do not receive MDR-TB treatment. We used boot strapping to estimate 95% uncertainty intervals.

Potential impact of contact investigations

We used a method previously published by Yuen et al. to estimate the number of children who could be diagnosed with MDR-TB if household contact investigations were performed around all adults currently being treated for MDR-TB[11]. As a starting point, we used country-level reports of the number of people started on MDR-TB treatment in 2015[3]. Because publicly available country-level reports do not disaggregate this number by age, we assumed that all people reported to have started MDR-TB treatment represent adult source cases; we believed this assumption to be justified given that fewer than 1,000 children received MDR-TB treatment in 2015, comprising less than 1% of the 125,000 people who started MDR-TB treatment that year. For each country, we multiplied the number of people who started MDR-TB treatment by a country-specific estimate of the average number of children per household and non-country-specific estimates of the risks of TB disease and infection in child household contacts of TB patients[12]. We thus produced estimates of the number of children expected to be diagnosed with presumptive MDR-TB as a result of contact investigations and the number of children expected to be diagnosed with TB infection, presumed to be MDR-TB. We used boot strapping to calculate 95% uncertainty intervals. These methods are described in more detail elsewhere[11].

Results

Mortality in children with MDR-TB

Based on an annual incidence of 32,000 children developing MDR-TB each year, an estimated 6,758 (95% Uncertainty Interval (UI): 4,870 – 8,820) (21%) die; these include 59 (95% UI: 9 – 105) (5.9%) of the 1,000 who receive appropriate treatment and 6,700 (95% UI: 4,820 – 8,771) (22%) of the 31,000 who do not. Based on an annual incidence of 25,000 children developing MDR-TB each year, an estimated 5,425 (95% UI: 2,722 – 8,380) (22%) die; these include 59 (95% UI: 9 – 105) (5.9%) of the 1,000 who receive appropriate treatment and 5,364 (95% UI: 2,644 – 8,312) (22%) of the 24,000 who do not.

Potential impact of contact investigations

We estimate that performing household contact investigations around all adults currently being treated for MDR-TB globally would detect 4,344 (95% UI: 2,131 – 8,689) children aged under five years and 8,124 (95% UI: 2,723 – 24,026) children aged 5-14 years with presumptive MDR-TB disease. Global and regional estimates are shown in Table 1. In addition, contact investigations would identify an estimated 15,378 (95% UI: 12,570 – 18,954) children under five years old and 51,182 (95% UI: 39,558 – 65,957) aged 5-14 years with TB infection.

Discussion

Around 3% of children with TB have MDR-TB, amounting to between 25,000 and 32,000 children developing MDR-TB disease each year. Only 3–4% of them are diagnosed and treated and, as a result, around 21% of children with MDR-TB likely die. Increased implementation of household contact investigations could help to close the treatment gap. If household contact investigations were conducted around all adults diagnosed with MDR-TB, then over twelve times more children would be being diagnosed and treated than are currently being treated.

The paucity of information about children treated for MDR-TB leaves many important questions unanswered. Where are the largest gaps between incident disease and children treated? Which countries are missing the highest proportions or numbers of children with MDR-TB? Which age groups are most at risk of not being diagnosed and treated? To better understand the magnitude of the under-diagnosis and under-treatment of children with MDR-TB, the numbers of children who are currently being treated for MDR-TB should be included in official reports of the global TB epidemic. Not including these numbers in the current discourse around the global drug-resistant TB epidemic perpetuates the invisibility of these children, and makes it unlikely that their diagnosis and treatment will be prioritized by TB programs moving forward. Furthermore, to accurately understand the treatment gap, new country-level estimates of children with MDR-TB are warranted given that both existing estimates were based on information about the prevalence of drug resistance that existed before national drug resistance surveys in high-burden countries such as India, China, and Indonesia[13].

The evaluation of close (usually household) child contacts of adults known to have TB is a method proven to identify additional pediatric TB cases as well as children who would benefit from preventive therapy; however, contact investigation is underused in many countries[14,15]. Household contact investigations of adults being treated for MDR-TB could improve the treatment of pediatric MDR-TB cases substantially. Our estimates suggest that household contact investigations could identify 39–50% of the estimated number of children who develop MDR-TB each year. Given the difficulty in bacteriologically confirming TB diagnoses in children, most children diagnosed with TB through household contact investigations of adult MDR-TB patients would not themselves have drug susceptibility test results. However, given the general concordance between drug resistance profiles among household members[16], presumptively treating these children for MDR-TB would be warranted, even though some degree of overtreatment would be inevitable. The extent to which contact investigation can close the treatment gap is dependent on the case detection and treatment rate for adults with MDR-TB. In settings with low diagnosis and treatment rates for adults, contact investigation alone will contribute little to closing the diagnostic gap for children. Thus, improving the detection and treatment of adults with MDR-TB is critical to improving the detection and treatment of children.

Household contact investigations also provide the opportunity to prevent future morbidity and mortality by identifying some of the estimated 2 million children (IQR: 1.6 million – 2.6 million) who are latently infected with multidrug-resistant TB strains. Children in the households of MDR-TB patients who have TB infection are at high risk of developing MDR-TB disease in the future. Although clinical trials are ongoing, observational data strongly suggest the effectiveness of preventive therapy in reducing the risk of progression of MDR-TB[17]. Alternatively, periodic evaluation of child contacts for 2 years can ensure that if they develop TB disease, they are diagnosed early and treated promptly with an effective regimen[18].

Conclusion

Large gaps exist in our knowledge of the pediatric MDR-TB epidemic. This lack of knowledge both reflects and perpetuates the lack of attention on children with MDR-TB. To save lives, TB programs must prioritize finding and treating children with MDR-TB. To help TB programs understand the magnitude of potential missed cases, current reporting systems should be revised to capture age-disaggregated data on patients treated for MDR-TB. Moreover, including specific information on children in reports on the global MDR-TB epidemic would help to highlight global and regional treatment gaps. The collection and use of increasingly granular data has been key to previous disease elimination programs[19] and is now needed to reduce morbidity and mortality due to pediatric MDR-TB.

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Table 1

Estimated incident pediatric MDR-TB cases, and the estimated number of children with MDR-TB who could be found through household contact investigations of adults starting MDR-TB treatment, by region. UI=Uncertainty Interval; CI=Confidence Interval

Region*	Estimated incident pediatric MDR-TB cases based on 2010 data (95% CI)†	Children <5 years old with MDR-TB in households of adult MDR-TB patients in 2015 (95% UI)	Children 5-14 years old with MDR-TB in households of adult MDR-TB patients in 2015 (95% UI)
Africa	4,736 (2,829 – 6,848)	1,035 (510 – 2,063)	1,909 (629 – 5,694)
Americas	606 (374 – 854)	150 (75 – 300)	285 (96 – 857)
Eastern Mediterranean	2,417 (339 – 5,087)	281 (140 – 567)	452 (151 – 1,346)
European	5,645 (4,206 – 7,463)	832 (394 – 1,634)	1,562 (557 – 4,388)
South-East Asia	10,000 (4,993 – 15,568)	1,593 (781 – 3,212)	2,970 (1,005 – 9,113)
Western Pacific	8,349 (5,639 – 11,610)	447 (219 – 903)	889 (296 – 2,667)
Global	31,948 (25,594 – 38,663)	4,350 (2,137 – 8,708)	8,082 (2,727 – 24,060)

*As defined by the World Health Organization

†From Jenkins at al, 2014[2]