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# Counting children with tuberculosis: why numbers matter

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SUMMARY

**In the last 5 years, childhood tuberculosis (TB) has received increasing attention from international organisations, national TB programmes and academics. For the first time, a number of different groups are developing techniques to estimate the burden of childhood TB. We review the challenges in diagnosing TB in children and the reasons why cases in children can go unreported. We discuss the importance of an accurate understanding of burden for identifying problems in programme delivery, targeting interventions, monitoring trends, setting targets, allocating resources appropriately and providing strong advocacy. We briefly review the estimates produced by new analytical methods, and outline the reasons for recent improvements in our understanding and potential future directions. We conclude that while innovation, collaboration and better data have improved our understanding of the childhood TB burden, it remains substantially incomplete.**

KEY WORDS: estimation; burden; TB; paediatric

CHILDHOOD TUBERCULOSIS (TB) has been neglected for many years by the international community. There has been a lack of interest from international agencies, national TB programmes (NTPs), clinicians, academics, advocates and funders. In March 2011, a meeting was convened in Stockholm to discuss childhood TB.[1] Over 110 participants, representing a wide variety of stakeholders, attended, and the group discussed the challenges in addressing childhood TB, as well as identifying key advocacy areas for development. The meeting resulted in a 'Call to Action for Childhood TB', which was endorsed by over 800 individuals and organisations in nearly 100 countries. Since then, interest in childhood TB has increased, resulting in greater visibility, funding, research and advocacy. In 2012, the World Health Organization (WHO) published its first estimate of the number of children who develop TB each year;[2] estimates are now reported annually, and the methodology used continues to evolve. In 2013, the WHO, in collaboration with other organisations such as the International Union Against Tuberculosis and Lung Disease (The Union) and the United Nations Children's Fund (UNICEF), published the International Roadmap for Childhood Tuberculosis.[3] As a critical first step in moving forward, the Roadmap highlighted the need to 'know your epidemic'. Also in 2013, the WHO and the Global Alliance for TB Drug Development (TB Alliance) organised a consultation to define and prioritise data gaps and analytical methods relevant to our understanding of the burden of childhood TB. This consultation shaped collaborations between relevant stakeholders and spurred the development of complementary analytical methods.[4]

This article discusses some of the challenges in estimating the childhood TB burden, describes the importance of robust estimates, considers the varied techniques used to arrive at estimates and discusses future directions. It uses the estimation of TB incidence in children as a case study for how a successful collaboration between institutions and academic groups can catalyse improvement in analytical methods. In this article, those aged <15 years are considered children.

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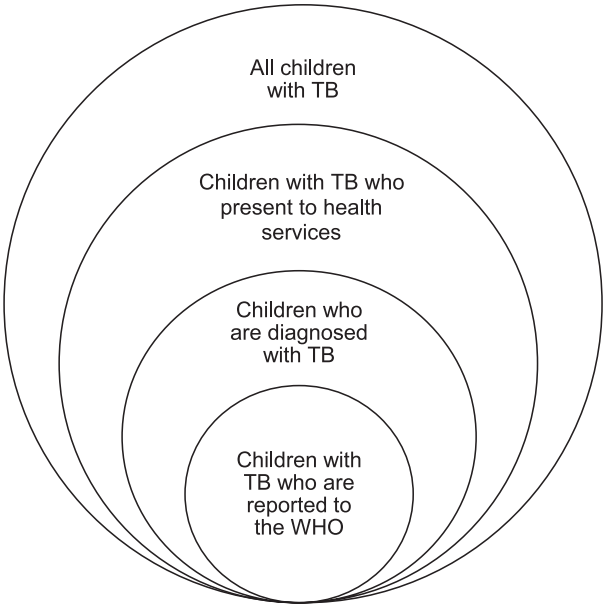


**Figure 1** The cascade from symptoms to reporting in children with tuberculosis. TB = tuberculosis; WHO = World Health Organization.

## CHALLENGES TO ESTIMATING THE BURDEN OF CHILDHOOD TUBERCULOSIS

In many settings, and particularly where TB is common, very few TB cases in children are bacteriologically confirmed, for a number of reasons: first, it can be challenging to obtain samples from young children for laboratory diagnosis; second, the paucibacillary nature of disease in many children means that the yield from bacteriological techniques such as smear microscopy is often low;[5,6] and finally, laboratory diagnosis with culture or Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) is usually not available in facilities where children present. Diagnosis therefore often relies upon clinical assessment supported by diagnostic tools (e.g., chest X-ray) that have significant limitations in specificity and sensitivity.[7,8] A large number of children with TB are therefore likely to remain undiagnosed each year. In addition to diagnostic uncertainties, a major challenge for estimating burden is under-reporting. Until recently, NTPs of most TB-endemic countries were required to report only sputum smear-positive cases, and would report children in a broad age category of 0–14 years. This led to the perception (or misperception) that the TB burden in children was low. NTPs are now requested to report all TB cases and by two age bands for children (0–4 years and 5–14 years). However, the NTP can only report data for children who are registered with the NTP at the time of diagnosis. Unfortunately, a large but unknown number of children are treated for TB but are not registered with the NTP.[9,10]

The challenges of confirming diagnosis are greatest in infants and young children (age <5 years); importantly, this age group also has an increased risk of severe disease and TB-related mortality. Although uncomplicated lymph node disease is common in children, a substantial proportion also develop severe forms of disseminated TB, such as miliary TB or TB meningitis,[11] which are associated with significant morbidity and mortality,[12,13] or present with concomitant severe pneumonia or malnutrition.[14] Finally, from a public health viewpoint, it is important to recognise that children can transmit TB to contacts, especially older children and adolescents, who often develop adult-type or cavitary TB that is highly infectious.[15–19]

## WHAT IS MEANT BY DISEASE BURDEN?

The term 'disease burden' describes the number and the associated rate of individuals in a community with a particular condition and its consequences for morbidity, disability and mortality. Traditionally, in the field of TB, incidence, prevalence and mortality have all been estimated and reported as measures of disease burden. The three measures are related, and although each requires a different estimation approach, comparison between the three allows verification of internal consistency. The three measures tell us different things about the epidemic. Incidence refers to the number of individuals who develop TB each year, prevalence the number at a given time point who have TB, and mortality the number who die each year with TB thought to be the primary cause. To take into account the size of the population in reference, and to compare across communities and with other diseases, the corresponding incidence, prevalence and mortality rates are also calculated.

## THE IMPORTANCE OF ESTIMATES

Accurate and reliable childhood TB incidence estimates, when compared with the number of reported and treated cases from national surveillance systems, quantify the degree to which children with TB are not being found, diagnosed or treated. This may help to identify weak links in the cascade from symptoms to presentation to diagnosis to treatment to official notification (Figure 1). Investigation of these links may then suggest actions to improve case detection and reporting. Discrepancies in notifications or quality of detection and reporting among epidemiologically similar settings may alert programmes to existing problems and provide new insights into how these problems may be resolved. Specific programmatic indices may also give a crude indication of overall childhood TB management (Table 1).

As children can only have been infected in the few years since birth, and as most progression is within 12 months,[20] TB in children represents recent transmission. Childhood TB therefore also provides an insight

**Table 1** Programmatic indicators that may give an indication of how well childhood TB is being diagnosed and reported

| Indicator | Approximate expected value* | Likely interpretation if: | |
|---|---|---|---|
| | | Too high | Too low |
| Proportion of overall burden found in children | 5–20%, increasing with overall TB incidence | Overdiagnosis of childhood TB | Underdiagnosis of childhood TB |
| Proportion of treated paediatric cases with a confirmed diagnosis | 20–30%, increasing with age and resources | Not enough children treated on clinical grounds | Not enough effort made to confirm the diagnosis |
| Proportion of paediatric cases that are sputum smear-positive† | 10% in 0–14 age group as a whole | Not enough children treated on clinical grounds | Not enough effort made to confirm the diagnosis |
| Proportion paediatric cases aged <5 years | Slightly over 50% | Too many young children being treated clinically | Only older children with 'classic' symptoms being treated or only children with confirmed disease treated |
| Proportion of paediatric cases that are EPTB | 10% in 0–14 age group as a whole; 25% in the 0–4 age group | Children with various clinical characteristics, such as cervical lymphadenopathy, being diagnosed with TB when many do not have TB | Only confirmed cases (which are frequently PTB) classified as TB |

* These provide a rule-of-thumb or guide only. Enormous variability in these parameters has been described in studies across different settings.
† Since 2013, cases are now reported to the WHO according to whether bacteriologically confirmed, which includes confirmation by smear microscopy, culture and Xpert® MTB/RIF.
TB = tuberculosis; EPTB = extra-pulmonary TB; PTB = pulmonary TB; WHO = World Health Organization.

into which strains of *Mycobacterium tuberculosis* are currently circulating in a community, including drug-resistant strains. TB incidence in children reflects local transmission rates, and is therefore a potential indicator for TB control in general.[21] Accurate baseline numbers and trends over time allow appropriate national and global targets to be set, and assessment of whether these are met.

Robust estimates help inform service planning, resource allocation and the targeting of interventions to where they are needed most. In addition, they permit an appropriate assessment of the potential market for new diagnostics, vaccines and drugs. Industry, academic funding organisations, development agencies, non-governmental organisations and NTPs all want to make rational investment decisions, and burden quantification is therefore an essential component in engaging with them. Furthermore, for the purposes of advocacy, knowing the burden of disease is a tool to raise the profile of these vulnerable children and motivate better diagnostics, treatments, funding, rights, support or recognition. The importance of accurate estimates is summarised in Table 2.

## METHODOLOGY FOR ESTIMATION OF CHILDHOOD TUBERCULOSIS INCIDENCE

Until recently, the WHO did not publish separate childhood TB estimates, partly due to difficulties in interpreting notification data for children, and partly because many countries did not then disaggregate notifications by age. Over the last 10 years, the number of countries reporting disaggregated data has sharply increased (Figure 2). The WHO published its first official estimate in 2012.[2] As a starting point, they followed a two-step procedure (Figure 3), first estimating paediatric notifications for countries that did not disaggregate by age, and then estimating the underlying incidence through dividing notifications by a case detection ratio (CDR). This procedure gave a global childhood TB incidence estimate of 490 000 (range 470 000–510 000), equivalent to about 6% of the total number of 8.7 million incident cases in 2011.[2] Acknowledged limitations included the assumption that the paediatric CDR was the same as the CDR for adults (66%, range 64–69), that there had been no misclassification of TB in paediatric notifications and that the proportion of TB burden among children was the same regardless of whether or not countries disaggregated notifications by age. Commentators were concerned that the assumption of an equal CDR for adults and children was at odds with observational evidence of under-reporting and under-diagnosis,[9,10] and that it would lead to an underestimated estimate of paediatric incidence.

More recently, other groups have used complementary methods to estimate the TB burden in children. Jenkins et al.[22] followed a different procedure based on using the expected proportion of smear-positive cases in each age group[23] to obtain an adjusted proportion of TB incidence among children (Figure 4). A regression of the proportion of TB in children against total incidence[24] was then used to predict this proportion in countries not disaggregating notifications by age. Finally, these country-level proportions were multiplied by the WHO total country TB estimates and aggregated to predict that 999 792 (95% uncertainty interval [UI] 937 877–1 055 414) children developed TB in 2010. Limitations of this approach include the shortcomings of notification data

**Table 2** Reasons for the importance of more accurate estimates of the childhood TB burden

| Needs for better estimates | Rationale for better estimates |
|---|---|
| Political engagement and political will | Accurate data of the child TB burden are required to engage the leadership and support the TB control sector, the child health sector, government health ministries, advocacy groups and the wider community |
| Inform situational analysis and identify gaps | It is critical to 'know your epidemic' to identify current gaps and challenges as well as priorities for implementation to address child TB |
| Child TB is an indicator of recent transmission | Accurate data on TB in young children monitored over time could be an important TB control indicator, as a sensitive indicator of recent transmission and an early indicator of transmission 'hot spots' |
| Resource allocation for health systems and NTP | The numbers of children with drug-susceptible and drug-resistant TB will inform health service and human resource requirements to ensure effective programmatic management |
| Procurement needs of diagnostics and therapeutics | The numbers of children with drug-sensitive and drug-resistant tuberculosis will inform the needs and sufficient procurement of diagnostic tools and anti-tuberculosis medication, including medication suitable for young children. |
| Engage the maternal and child health sector | Data that show the importance of TB in the context of child morbidity and mortality are required to engage the leadership and support of the maternal and child health sector and government, especially as most countries include child health as a major national priority |
| Advocacy and engagement of civil society | Accurate data about the TB burden with direct and indirect consequences on child health are extremely valuable for advocacy groups, national champions and civil society to highlight the need for action |
| Monitoring and evaluation tool | Accurate baseline data are required to monitor and evaluate implementation of activities aiming to improve the detection, prevention and management of child TB |
| Identification of needs and improves quality of research | Accurate data would greatly strengthen the many opportunities for operational research in children as well as the quality of clinical trials that evaluate novel diagnostics or therapeutic regimens |
| Potential for investment in novel diagnostics and therapeutics | The potential 'size of the market' is an important factor that informs investment in research and development of novel diagnostics and therapeutics |

TB = tuberculosis; NTP = National TB Programme.

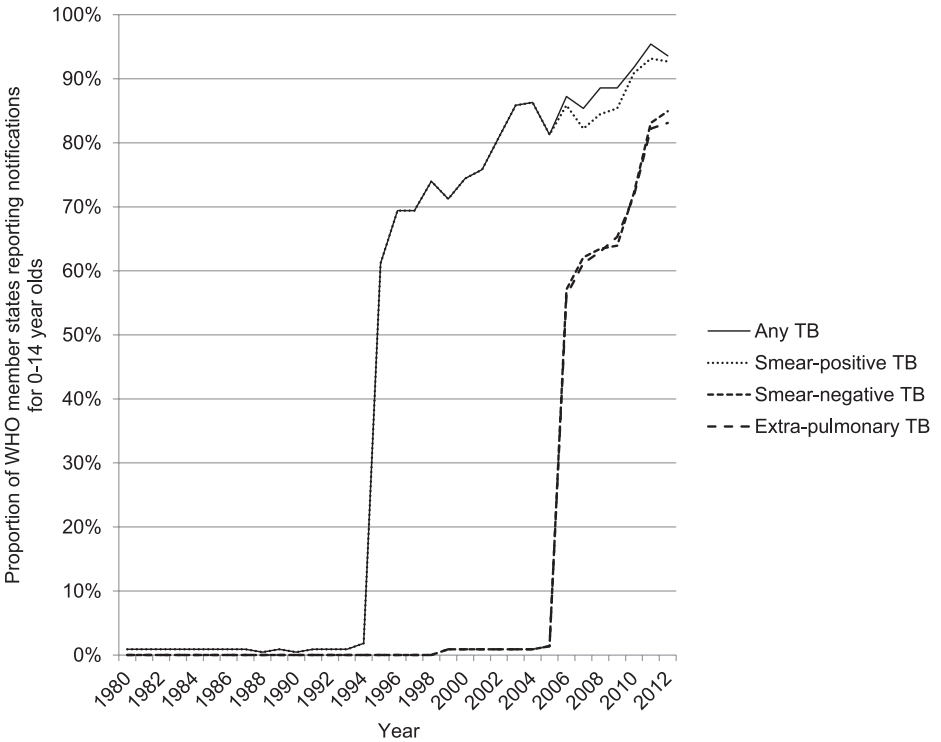


**Figure 2** Improvements in age-disaggregated case reporting between 1990 and 2012. WHO = World Health Organization.

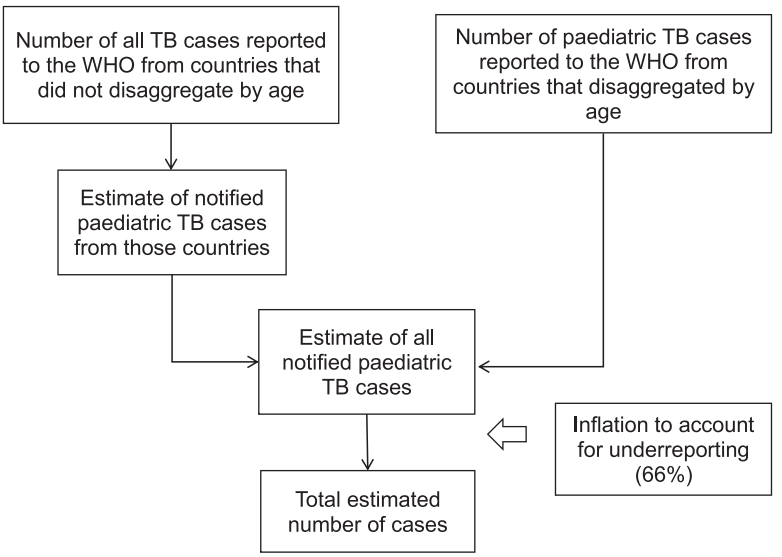


**Figure 3** Methodology employed by the WHO to estimate TB incidence in children. TB = tuberculosis; WHO = World Health Organization.

and the challenges in estimating TB incidence,[25] which represent sources of error and uncertainty that are not captured in the UI of this paediatric TB estimate. Furthermore, the assumption that the age-specific proportions of TB cases that are smear-positive from previous studies[23] are representative of the present day proportions across all countries requires further review; such an effort is currently in progress.[26] If countries replace smear microscopy with other diagnostic tools, this estimation method may need to be modified to account for the age-specific operation characteristics of those tools.

Dodd et al. used a mathematical modelling approach to produce an estimate independent of paediatric notifications,[27] initially focusing on the 22 high-burden countries in 2010. Demographic data and WHO TB prevalence estimates were used to predict the incidence of tuberculous infection in children. An age-dependent model of progression to extra-pulmonary TB and pulmonary TB was then used to estimate the incidence of disease, taking into account country-level bacille Calmette-Guérin (BCG) vaccination coverage and human immunodeficiency virus (HIV) prevalence (Figure 5). This resulted in a global estimate for childhood TB incidence for 2013 of a median of 827 000 cases (interquartile range [IQR] 549 000–1 245 000). Limitations include shortcomings in adult TB prevalence estimates, uncertainty around the impact of BCG and HIV, and the applicability of data from the literature to present-day risk of disease progression.

The Institute of Health Metrics and Evaluation (IHME) also produces estimates for childhood TB,[28] as part of the Global Burden of Disease (GBD)

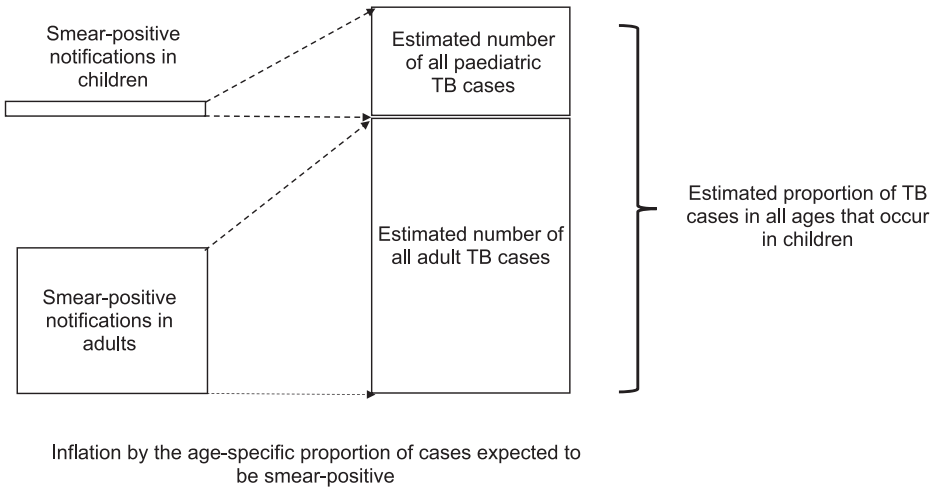


**Figure 4** Methodology employed by Jenkins et al. in estimating TB in children.[22] TB = tuberculosis.

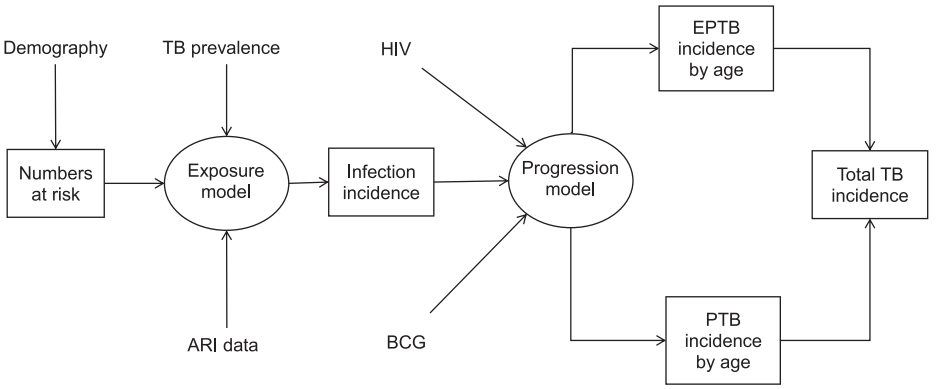


**Figure 5** Methodology employed by Dodd et al. in estimating TB in children.[27] TB = tuberculosis; ARI = annual risk of infection; HIV = human immunodeficiency virus; BCG = bacille Calmette-Guérin; EPTB = extra-pulmonary TB; PTB = pulmonary TB.

study[29,30] with mortality, prevalence and incidence estimated to be internally consistent. Mortality estimates rely on vital registration and verbal autopsy data. Under-recognition of TB is likely to lead to an underestimate of TB as a cause of death in children in vital registration data. The challenges of identifying TB from standardised verbal autopsy interviews with relatives have additional limitations; however, the errors from low sensitivity and specificity partially cancel out at the level of population estimates.[31] Estimates of prevalence and incidence of childhood TB are made using data from prevalence surveys, notification data and the addition of the GBD mortality estimates in a Bayesian meta-regression tool, DisMod-MR 2.0 (Department of Public Health, Erasmus University, Rotterdam, the Netherlands). The differential equations built into DisMod-MR 2.0 force consistency in the estimates of incidence, prevalence and TB mortality rates. In children aged 0–14 years, 187 944 (95%UI 181 637–193 832) incident cases of TB were estimated globally in 2013. With few observed prevalence data points, these estimates rely heavily on the notification data with the above-mentioned limitations of under-diagnosis of TB in childhood, the application of a coarse case detection rate by country at all ages and the lack of age, sex and type of TB detail in most notification data.

In 2015, the WHO used an ensemble approach to estimate paediatric TB incidence,[32] producing a weighted average of 1) their notification-based estimate, with adjustment using methodology from Jenkins et al.,[22] and 2) the estimate derived from the mathematical model by Dodd et al.[27] The resulting estimate of global TB incidence among children in 2014 was 1 000 000 (range 900 000–1 100 000), equivalent to about 10% of the total number of 9.6 million incident cases.

## ESTIMATING DRUG-RESISTANT TUBERCULOSIS

Jenkins et al. also estimated the burden of multidrug-resistant TB (MDR-TB) in children. Their systematic review evaluated a linear association between the proportion of MDR-TB in children and treatment-naïve adults. Combined with their estimates of childhood TB incidence, this implied that 31 948 (95%UI 25 594–38 663) children developed MDR-TB in 2010.[22] In a subsequent study, Yuen et al. undertook a systematic review of the proportion of paediatric cases that were isoniazid (INH) resistant in 2010.[33] The group estimated that 12.1% (95%UI 9.8–14.8) of all children with TB have INH-resistant disease, resulting in 120 872 (95%UI 96 628–149 059) incident cases in 2010.[34]

## THE CHANGING LANDSCAPE OF BURDEN ESTIMATION

Estimates for childhood TB burden are improving for several reasons. First, a number of different, complementary approaches have been taken. The existence of these disparate methods and collaboration between the groups that have developed them provide an opportunity to scrutinise and understand differences in estimates in order to refine and improve methods. Second, increased training, education and policy changes mean more paediatric cases are being identified, registered and reported, and non-bacteriologically confirmed cases are increasingly being entered into registers. Third, the number of countries that disaggregate data by age has increased. Fourth, many countries have developed paediatric TB committees or subgroups within the NTP and age-specific indicators have been promoted in a number of settings. Fifth, inventory (or capture-recapture) studies to determine the discrepancy between treated cases and reported cases are being conducted in several countries, and will give valuable data in countries with a large private health provider sector. Sixth, electronic reporting of data is more widespread, improving accuracy and completeness. Seventh, more surveys, better surveillance and an increased number of academic studies are being conducted on childhood TB to improve primary data

sources. Finally, children who died due to TB in hospitals were frequently not registered with NTPs; this is improving.

Scientific developments in diagnostics may increase the number of children who are diagnosed, treated and reported to NTPs. A recent evaluation of the Xpert test in children found it to be more sensitive than sputum smear microscopy.[6] An RNA gene expression study has identified a unique 'signature' in the immune response that, if converted into a point-of-care test, could improve our ability to diagnose TB in children.[35]

In 2013, TB Alliance was awarded US$16.7 million from UNITAID to develop child-friendly formulations for TB drugs for children.[36] Part of this project is to quantify the potential market for first- and second-line anti-tuberculosis drugs for children in order to engage with pharmaceutical companies. This funding, as well as providing estimates of market, has funded additional work into estimating and describing the TB burden in children.

NTP reviews have been one of the motivating factors used to drive change in national TB policy to identify, treat and report childhood TB. In many countries, funding from the Global Fund is contingent on demonstrating responses to suggestions made in NTP reviews. There are increasingly paediatric TB specialists on the team who conduct these reviews and evaluate paediatric-specific indicators. The specialists then provide suggestions and targets specifically for childhood TB.

## FUTURE PERSPECTIVES

Increased use of modelling and better data on which to build models will improve the accuracy of new estimates. It is also possible to use modelling to identify which data inputs contribute most to uncertainty in overall estimates. Such analysis can consequently help prioritise areas of primary data collection for improving the accuracy of estimates. Comparison and synthesis of modelling methodology will also help. Assessing these estimates over time also allows an appreciation of changing trends. Ideally, further disaggregation of reported data would take place so that children are reported in 5-year age-bands (0–4 years, 5–9 years and 10–14 years). In addition, the inclusion of children into appropriately designed prevalence surveys would allow a better grasp of primary data, and lead to better-validated models. Children have not been included in prevalence surveys due to a number of logistical, financial and ethical challenges.[37,38] However, it may be possible to include children, using a modified approach, in certain sentinel sites. Many investigators, policy makers and public health experts, including the authors of this article, are currently working on how this could be done in practice, with the aim of producing clear protocols and algorithms. As we move from the Millennium Development Goals to the Sustainable Development Goals, there is the opportunity to critically review how prevalence surveys are conducted, including how to include children, as well as how to incorporate newer diagnostic methods. As estimates become more accurate and modelling becomes more sophisticated, it will be possible to model the impact of interventions on the burden of childhood TB. Sound estimates of both the cost and cost-effectiveness of these interventions will provide information and powerful motivation to policy makers and politicians.

## CONCLUSION

Collaboration among the WHO, The Union, the Child Health Epidemiology Reference Group (CHERG), IHME, TB Alliance and different academic groups has greatly improved our understanding of the burden of childhood TB in the last couple of years. New and innovative methods are being used to estimate burden and improvements in reporting are being seen. There has been increased investment and significant progresses in scientific research. However, we are still some way from a complete understanding of which children get TB and how best to find them.

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## RESUME

**Au cours des 5 dernières années, la tuberculose (TB) de l'enfant a fait l'objet d'une attention accrue de la part des organisations internationales, des programmes nationaux TB et des universitaires. Pour la première fois, plusieurs groupes différents sont en train d'élaborer des techniques visant à estimer le poids de la TB de l'enfant. Nous revoyons les défis du diagnostic de la TB chez les enfants et les raisons pour lesquelles les cas de TB des enfants peuvent ne pas être déclarés. Nous discutons de l'importance d'une connaissance précise du fardeau pour identifier les problèmes relatifs à l'exécution des programmes, au ciblage des interventions, au suivi des tendances, au choix des objectifs, à la répartition appropriée des ressources et à un plaidoyer convaincant. Nous revoyons rapidement les estimations produites par de nouvelles méthodes d'analyse, et nous exposons les raisons des récentes améliorations de notre compréhension et les potentielles orientations futures. Nous concluons que même si les innovations, la collaboration et de meilleures données ont amélioré notre connaissance du fardeau de la TB de l'enfant, le tableau reste néanmoins assez incomplet.**

## RESUMEN

**En los últimos 5 años las organizaciones internacionales, los programas nacionales contra la tuberculosis (TB) y el sector académico han prestado cada vez mayor atención a la TB de los niños. Por primera vez varios grupos diferentes están desarrollando técnicas encaminadas a estimar la carga de morbilidad por TB en la esfera pediátrica. En el presente artículo se examinan las dificultades que plantea el diagnóstico de la enfermedad en este grupo de edad y las razones de la subnotificación de los casos de TB en los niños. Se analiza la importancia de comprender de manera precisa la carga de morbilidad cuando se busca detectar los problemas en la ejecución de los programas, la definición de las poblaciones destinatarias de las intervenciones, la vigilancia de las tendencias, la fijación de los objetivos, la atribución adecuada de los recursos y llevar a cabo una promoción decisiva de la causa. Se evalúan en forma concisa las estimaciones obtenidas mediante los nuevos métodos analíticos, se sintetizan las razones de los progresos recientes en el conocimiento y se proponen direcciones posibles de las actividades en el futuro. En conclusión, se considera que aunque la innovación, la colaboración y el hecho de contar con datos de mejor calidad han contribuido a una mayor comprensión de la carga de morbilidad por la TB en los niños, quedan aún lagunas considerables en este campo.**