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Title Page

Manuscript Title

Counting Children with Tuberculosis: Why Numbers Matter

Authors and Affiliations

James A Seddon[1]
Helen E Jenkins[2]
Li Liu[3,4]
Ted Cohen[5]
Robert E Black[3]
Theo Vos[6]
Mercedes C. Becerra[7]
Stephen M Graham[8,9,10]
Charalambos Sismanidis[11]
Peter J Dodd[12]

[1]Department of Paediatrics, Imperial College London, London, UK
[2]Department of Global Health Equity, Brigham and Women's Hospital, Boston, USA
[3]Institute for International Programs, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA
[4]Department of Population, Family, and Reproductive Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA
[5]Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, USA
[6]Institute for Health Metrics and Evaluation, University of Washington, Seattle, USA
[7]Department of Global Health and Social Medicine, Harvard Medical School, Boston, USA
[8]Centre for International Child Health, University of Melbourne Department of Paediatrics and Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Australia
[9]International Union Against Tuberculosis and Lung Disease, Paris, France
[10]The Burnet Institute, Melbourne, Australia

[11]Global TB Programme, World Health Organization, Geneva, Switzerland

[12]School of Health and Related Research, University of Sheffield, Sheffield, UK

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Corresponding Author

Dr James A Seddon

Department of Paediatrics

Imperial College London

Norfolk Place

London W2 1PG

United Kingdom

Email: james.seddon@imperial.ac.uk

Summary

In the last five 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 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, 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 childhood TB burden, it remains substantially incomplete.

Introduction

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 attended representing a wide variety of stakeholders 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 their first estimate of the number of children that 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 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 childhood TB burden. 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 burden of childhood TB, 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. Within the article children are considered as those aged less than fifteen years.

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, and laboratory diagnosis with culture or Xpert MTB/RIF 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 the diagnostic uncertainties, a major challenge for estimating burden is under-reporting. Until recently, NTPs of most TB endemic countries were required to only report 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 burden in children was low. NTPs are now requested to report all TB cases and by two age bands for children (0-4 years, 5-14 years). However, the NTP can only report data for those children that 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 (<5 years age); 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] that 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 require 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.

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 insight into which strains of *M. tuberculosis* are currently circulating in a community (including drug-resistant strains). TB incidence in children reflects local transmission rates, and therefore is a potential indicator for TB control more

generally.[21] Accurate baseline numbers and trends over time allow appropriate national and global targets to be set, and assessment of whether they are met.

Robust estimates help inform the 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. Further, for 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 ten 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 secondly estimating the underlying incidence through dividing notifications by a case detection ratio (CDR). Acknowledged limitations included the assumption that the paediatric CDR was the same as the CDR for adults (66%, range 64-69%); the assumption of no misclassification of TB in the paediatric notifications; and the assumption that the proportion of TB burden among children was the same whether countries disaggregated notifications by age or not. 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 would lead to an underestimated paediatric incidence estimate.

More recently, other groups have used complementary methods to estimate the TB burden in children. Jenkins and colleagues[22] followed a different procedure based on using the

198 expected proportion of smear-positive cases in each age group[23] to obtain an adjusted
199 proportion of TB incidence among children (Figure 4). A regression of the proportion of TB in
200 children against total incidence[24] was then used to predict this proportion in countries not
201 disaggregating notifications by age. Finally, these country-level proportions were multiplied
202 by the WHO total country TB estimates and aggregated to predict that 999,792 (95%
203 confidence interval: 937,877–1,055,414) children developed TB in 2010. Limitations of this
204 approach include the shortcomings of notification data and the challenges in estimating TB
205 incidence,[25] which represent sources of error and uncertainty that are not captured in the
206 confidence interval of this paediatric TB estimate. Furthermore, the assumption that the
207 age-specific proportions of TB cases that are smear-positive from previous studies[23] are
208 representative of the present day proportions across all countries requires further review;
209 such an effort is currently in progress.[26] If countries replace smear microscopy with other
210 diagnostic tools, this estimation method may need to be modified to account for the age-
211 specific operation characteristics of those tools
212
213 Dodd and colleagues used a mathematical modelling approach to produce an estimate
214 independent of paediatric notifications,[27] initially focussing on the twenty-two high-burden
215 countries in 2010. Demographic data and WHO TB prevalence estimates were used to
216 predict the incidence of TB infection in children. An age-dependent model of progression to
217 extra-pulmonary TB and pulmonary TB was then used to estimate the incidence of disease,
218 taking into account country-level BCG vaccination coverage and HIV prevalence (Figure 5).
219 This resulted in a global estimate for childhood TB incidence for 2013 of median 827,000
220 cases (IQR: 549,000-1,245,000). Limitations include shortcomings in adult TB prevalence
221 estimates, uncertainty around the impact of BCG and HIV, and the applicability of data from
222 the literature to present-day risk of disease progression.
223
224 The Institute of Health Metrics and Evaluation (IHME) also produce estimates for childhood
225 TB,[28] as part of the Global Burden of Disease (GBD) study[29,30] with mortality, prevalence and
226 incidence estimated simultaneously. Mortality estimates rely on vital registration and verbal
227 autopsy data, tools with associated challenges and limitations[31] Estimates of prevalence and
228 incidence of childhood TB are made using data from prevalence surveys, notification data
229 and the addition of the GBD mortality estimates in a Bayesian meta-regression tool,

DisMod-MR 2.0. The differential equations built into DisMod-MR 2.0 force consistency in the estimates of incidence, prevalence and TB mortality rates. In children 0-14 years old, 187,944 (181,637 to 193,832) incident cases of TB were estimated globally. 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 2014 WHO used an ensemble approach to estimate paediatric TB incidence,[32] producing a weighted average of their notification-based estimate and the estimate derived from the mathematical model by Dodd et al.[27] The resulting estimate of global TB incidence among children in 2013 was 550,000 (range 470,000-640,000), equivalent to about 6% of the total number of 9.0 million incident cases.

Drug-resistant tuberculosis estimation

Jenkins and colleagues also estimated the burden of multidrug-resistant (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 31,948 (IQR: 25,594-38,663) children developed MDR-TB in 2010.[22] In a subsequent study, Yuen and colleagues undertook a systematic review of the proportion of paediatric cases that were isoniazid-resistant in 2010.[33] The group estimated that 12.1% (95%CI: 9.8-14.8%) of all children with TB have isoniazid-resistant disease, resulting in 120,872 (95%CI: 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 the collaboration between the groups that have developed them, provide an opportunity to scrutinize 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; 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 sub-groups 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 heath-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 into childhood TB to improve primary data sources. Finally, children who died of TB in hospital 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. Recently, Xpert MTB/RIF was evaluated in children and was found 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 USD16.7 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 TB 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 burden of TB in children.

NTP reviews have been one of the motivating factors used to drive through 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. Increasingly there are paediatric TB specialists on the team that conducts 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 the uncertainty in the overall estimates. Such analysis can consequently hep prioritize 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 five-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 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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Table 1: Programmatic indicators that may give an indication of how well childhood tuberculosis is being diagnosed and reported

Indicator	Approximate expected value[1]	Likely interpretation if:	
		Too high	Too low
Proportion of overall burden found in children	5%-20%, increasing with overall TB incidence	Over-diagnosis of childhood TB	Under-diagnosis 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[2]	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 that are under-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 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

TB: tuberculosis; EPTB: extra-pulmonary tuberculosis

[1]These expected values provide a rule-of-thumb or guide only. Enormous variability in these parameters has been described in studies across different settings

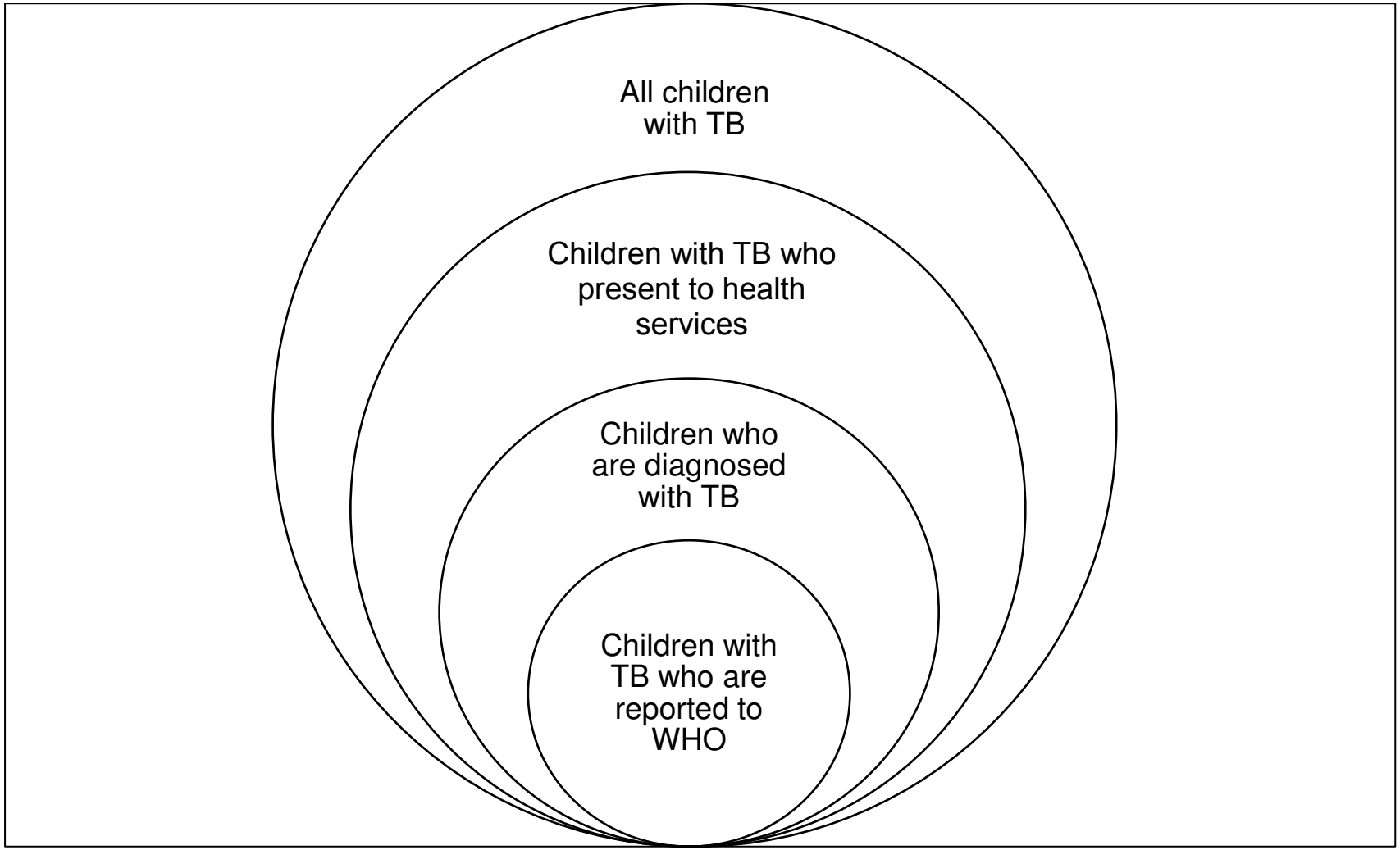
[2]Since 2013, cases are now reported to WHO according to whether bacteriologically confirmed, which includes confirmation by smear microscopy, culture and Xpert MTB/RIF

Table 2: Reasons for the importance of more accurate estimates of the burden of childhood tuberculosis

Needs for better estimates	Rationale for better estimates
Political engagement and political will	Accurate data of the burden of tuberculosis in children are required to engage the leadership and support of the tuberculosis 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" in order to identify current gaps and challenges as well as priorities for implementation to address child tuberculosis.
Child TB is an indicator for surveillance of recent transmission	Accurate data of tuberculosis in young children monitored over time could be an important tuberculosis 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-sensitive and drug-resistant tuberculosis 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 tuberculosis 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 of the burden of tuberculosis 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 tuberculosis.
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 one important factor that informs investment in research and development of novel diagnostics and therapeutics.

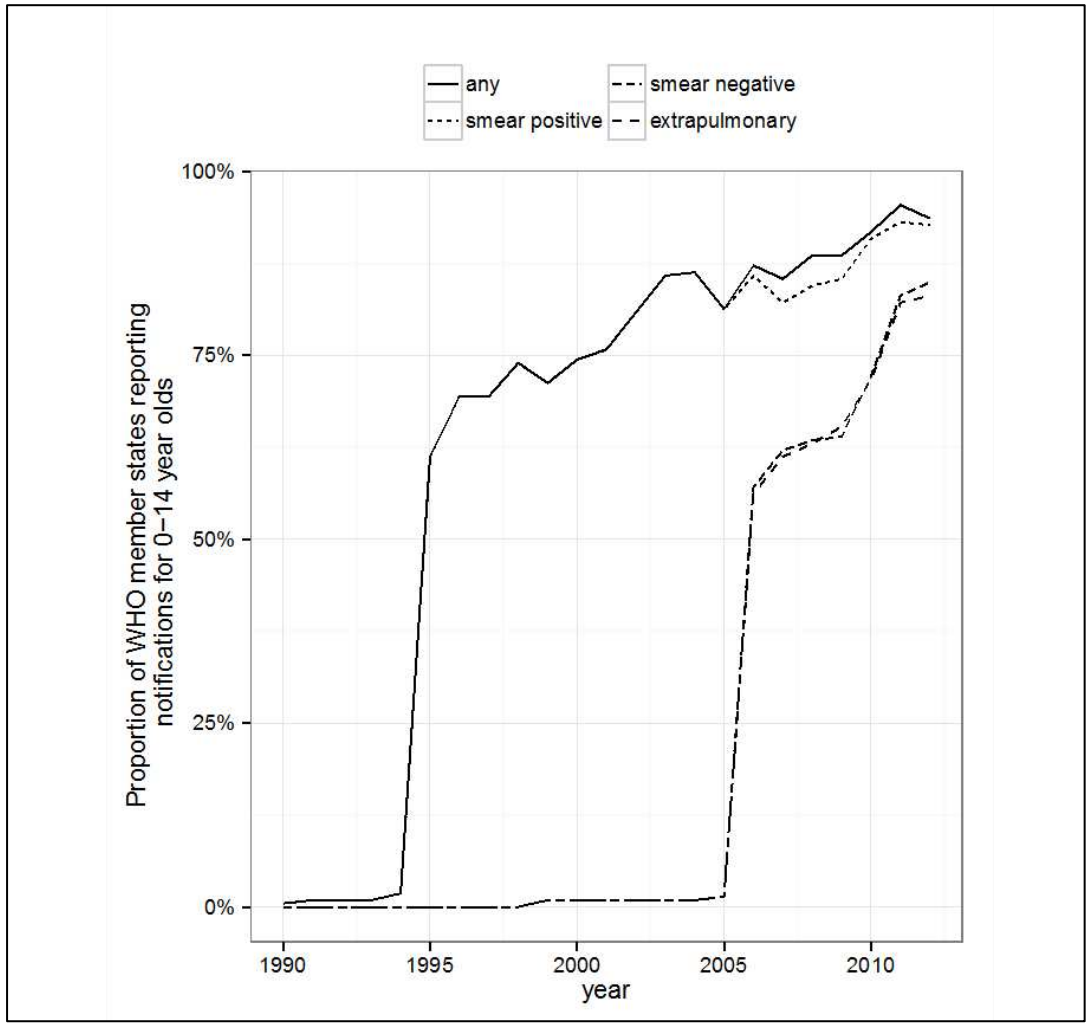
TB: tuberculosis; NTP: National TB Programme

Figure 1: The cascade from symptoms to reporting in children with tuberculosis



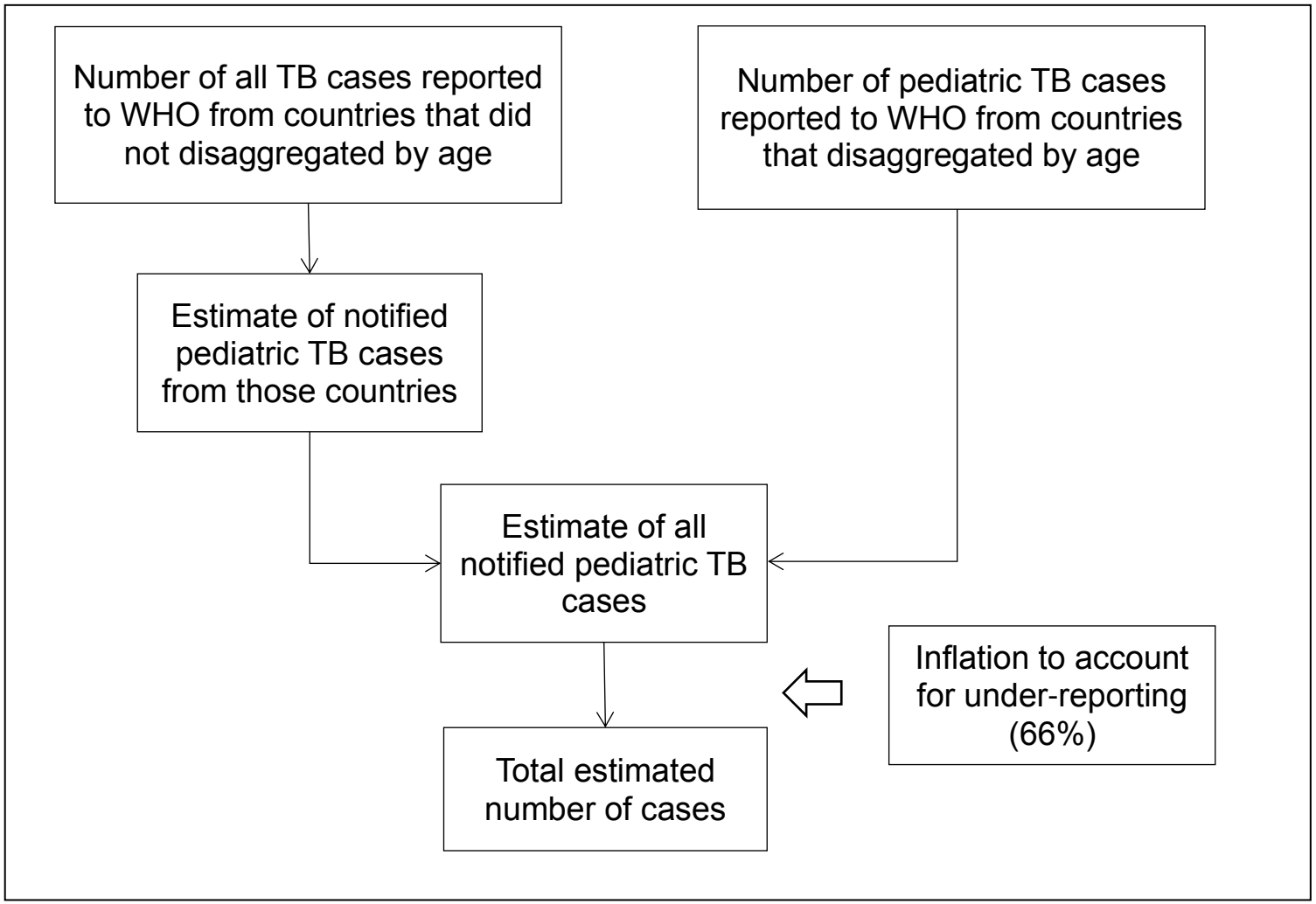
TB: tuberculosis; WHO: World Health Organization

Figure 2: Improvements in age-disaggregated case reporting between 1990 and 2012



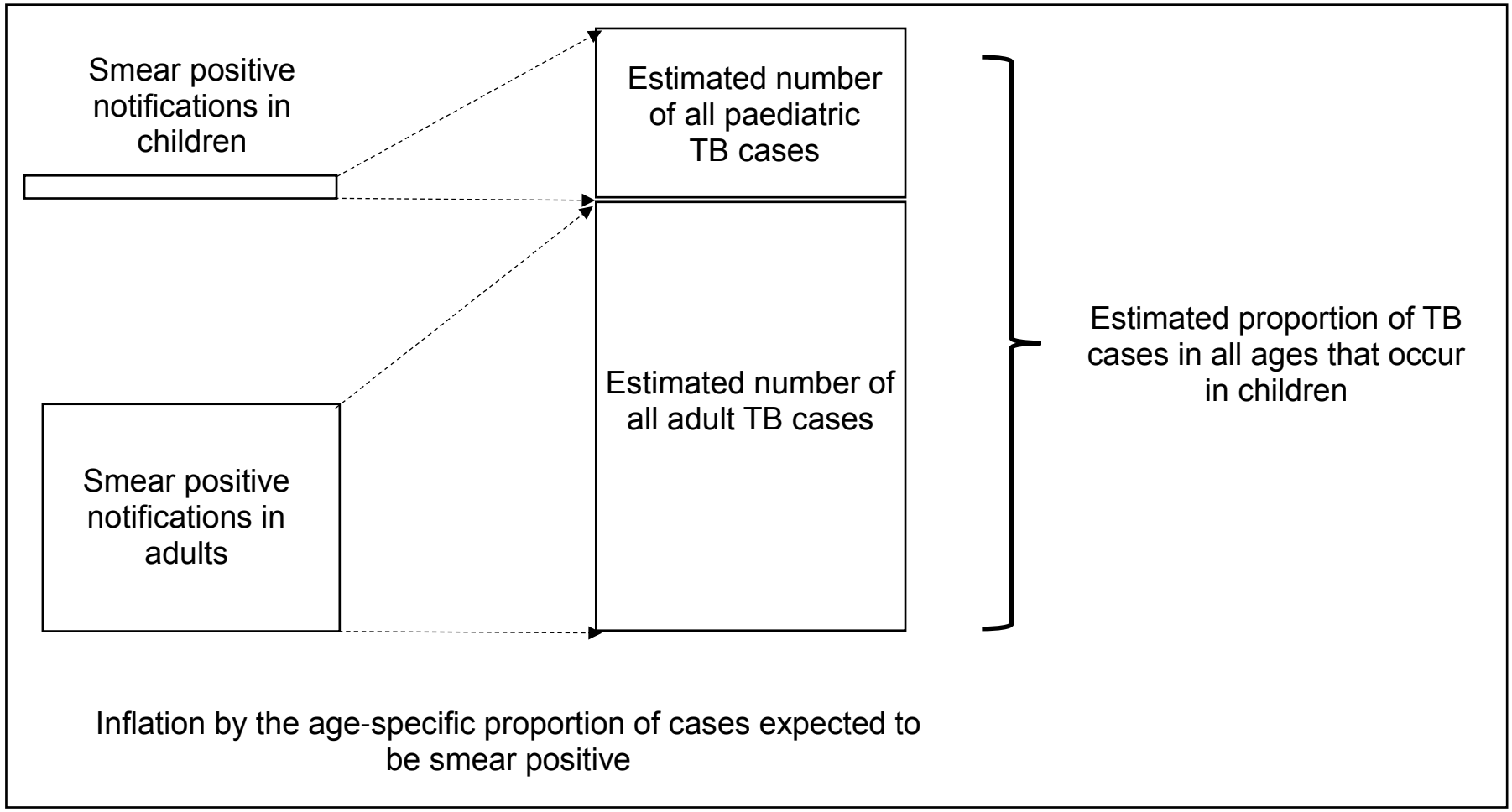
WHO: World Health Organization

Figure 3: Methodology employed by the World Health Organization to estimate the incidence of tuberculosis in children



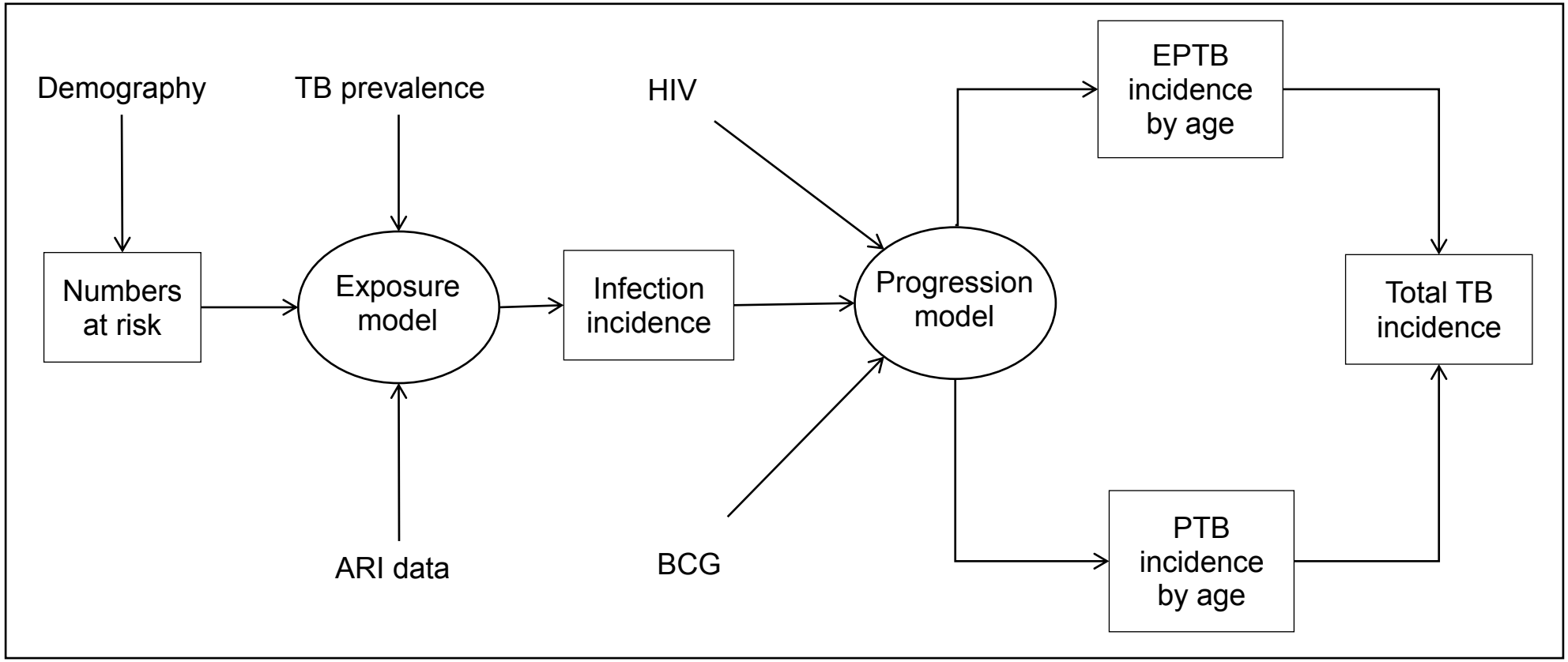
TB: tuberculosis; WHO: World Health Organization

Figure 4: Methodology employed by Jenkins et al. in the estimation of tuberculosis in children



TB: tuberculosis

Figure 5: Methodology employed by Dodd et al. in the estimation of tuberculosis in children



TB: tuberculosis; ARI: annual risk of infection; HIV: human immunodeficiency virus; BCG: Bacillus Calmette–Guérin; EPTB: extra-pulmonary tuberculosis; PTB: pulmonary tuberculosis