CHILDREN

STOP TB

KEY POPULATIONS BRIEF

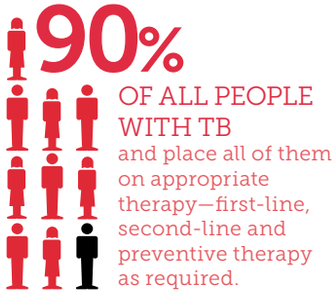
Stop TB Partnership

Childhood TB has been called a "sentinel event" because it indicates failure on two fronts (1). First, it signals an ongoing transmission, since the child likely contracted TB from someone close to him or her and who has likely remained untreated. Second, it indicates a wider failure in the system, since it points to the lack of preventative therapy that could have easily stopped the child from developing TB in the first place (1). Because of the diagnostic challenges presented by childhood TB, symptoms are often missed. Missed or late diagnosis can have catastrophic health impacts for the child and increase the chance of mortality. Suboptimal diagnostic methods, poor screening compliance, and unrealistic treatment guidelines mean that children face even greater barriers to accessing care than adults, making this population even harder to reach. Children often exist as a vulnerable population within already vulnerable populations. Therefore, it is imperative that TB finally be addressed head-on by policy makers, civil society, and health professionals. Not only do children provide the reservoir from which future cases will develop, but continued inaction is costing lives.

Global Plan to End TB and key populations

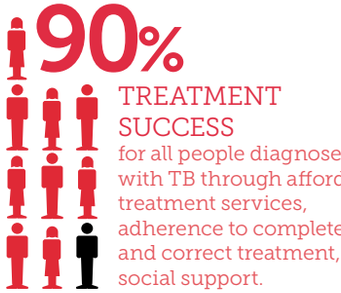
The Global Plan to End TB outlines a number of key targets to be achieved by 2020, or 2025 at the latest. The plan refers to people who are vulnerable, underserved or at risk as TB "key populations" and provides models for investment packages that will allow countries to achieve the 90-(90)-90 targets[1]. The Plan also suggests that all countries:

Reach at least



As a part of this approach, reach at least

Achieve at least

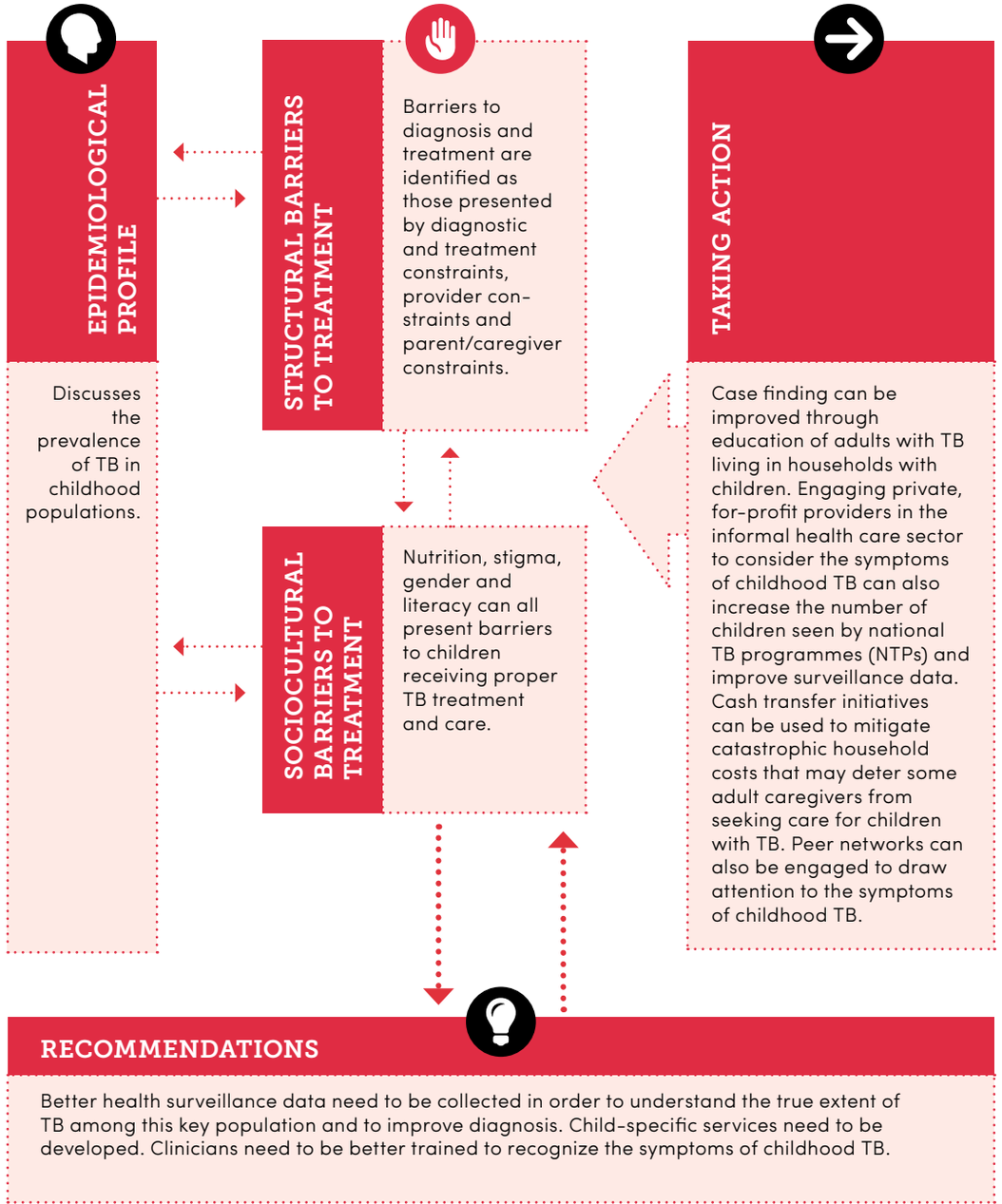


- Identify their key populations at national and subnational levels according to estimates of the risks faced, population size, and particular barriers, including human rights and gender-related barriers, to accessing TB care;
- Set an operational target of reaching at least 90% of people in key populations through improved access to services, rights-based systematic screening where required and new case-finding methods, and providing all people in need with effective and affordable treatment;
- Report on progress with respect to TB using data that are disaggregated by key population;
- Ensure the active participation of key populations in the development and delivery of services and the provision of TB care in safe and respectful environments.

This guide utilizes the above recommendations in order to outline the risks and barriers to access, discuss strategies for improved access, and highlight opportunities for the involvement of children and their caregivers in all stages of programme development and service delivery.

1 The 90-(90)-90 plan calls on NTPs to aim to reach 90% of all people with TB and to start them on appropriate therapy. As part of this approach, countries should be reaching 90% of key populations. The final part of the strategy is to achieve at least 90% treat-ment success for all people diagnosed with TB.

What's in this guide?



Epidemiological profile

It is a challenge to estimate the prevalence of childhood TB because of poor case ascertainment, difficulties in diagnosis and inadequacies in current surveillance systems *(2–6)*. TB is harder to detect in children than in adults because of the poor sensitivity of traditional diagnostic tests and the fact that many childhood TB symptoms are non-specific *(7, 8)*. Children often have difficulties producing quality sputum samples, and smear microscopy – the method most commonly used to determine active TB in adult populations in low- and middle-income countries – yields even less accurate results in children than it does in adults *(2, 9–11)*. The World Health Organization (WHO) instead recommends a combination of clinical, non-microbiological and microbiological approaches to determine the presence of TB in both its latent and active form in children *(12)*. However, many of these tests, such as chest X-rays (CXR) and tuberculin skin tests (TSTs), are not available in low-resource settings, where TB is more likely to be endemic *(13)*. Furthermore, qualitative T-cell-based assays, such as TSTs, fail to distinguish between active and latent forms of TB in children *(9)*. Crucial missed opportunities for intervention mean that children are more vulnerable to the most severe forms of TB, with the disease often proving fatal *(14)*.

WHO estimates that in 2014 the TB incidence in children was 1.0 million *(15)*[2]. In this same year, there were an estimated 140,000 TB-related deaths among children *(15)*. However, given the lack of age-disaggregated national TB surveillance data, this could be a gross underestimation of the true burden of TB in this population *(6, 14, 16, 17)*. Age acts as an important variable in determining the risk of progressing to full disease following acquisition. Young children, particularly infants (<1yr.), are more susceptible to severe forms of TB and also at greater risk for death from the disease *(2, 9, 11)*. Background prevalence of TB in a community likely has the greatest influence on the risk of TB exposure in children *(11, 18)*. Community HIV dynamics are also a factor, with studies conducted in Zambia, Ethiopia and South Africa demonstrating a 20-fold increase in TB incidence among children living with HIV compared to HIV negative children *(16)*. Thus, many of the factors that contribute to the spread of TB in the adult population (poverty, migration, etc.) have an indirect impact on TB in children *(2)*.

2 WHO defines children as people aged <15. This age cutoff is used because it is consistent with the age categories for which notification data are reported nationally and with the cut-off used in current guidelines to define people eligible to participate in a TB prevalence survey (15).

Diagnostics and treatment constraints

Diagnostic challenges

The lack of a "gold standard" TB diagnostic test for children means that childhood TB is frequently under or misdiagnosed *(6)*. Diagnosis is made more challenging by the fact that up to 50% of children are thought to be asymptomatic during the early stage of TB (19). The presence of other diseases, such as HIV and pneumonia, also increases the likelihood of a missed or false diagnosis *(6, 20)*. Distinguishing between latent and active TB also presents a challenge for clinicians working with this population *(9, 21)*.

The combination of testing recommended by WHO to determine the presence of childhood TB is often not possible in low-resource settings; if it is possible, multiple visits to different health centres may be required, which can increase costs and leave children and their adult caregivers feeling as if they are being passed around the health service. These factors in turn increase loss to follow-up *(17)*. The new rapid diagnostic test, Xpert, also produces suboptimal results in children, which makes it vital that clinicians be attuned to the symptoms of childhood TB, rather than relying solely on diagnostic tools *(22, 23)*. Active TB in children is accompanied by persistent and non-remitting symptoms, such as a cough, meaning that symptom-based diagnosis is crucial for clinicians *(9)*. Missed or delayed diagnoses can have a devastating impact on health outcomes and often lead to the death of the child *(20, 24)*.

Challenges in anti-TB treatment and adherence

Anti-TB treatment has been shown to be as effective in children as it is in adults; however, it presents some specific challenges for children *(25)*. Children have traditionally not been included in drug trials for TB drugs, in part due to the lack of financial incentives for drug companies to include them and in part due to the challenges of measuring microbiological outcomes *(21)*. Children in resource-constrained settings have tended to receive portions of adult tablets, rather than liquid formulations or chewable tablets; these are both easier for children to swallow and for adult caregivers to administer, but have a shorter shelf-life *(5, 26)*. The method of crushing pills makes it harder to deliver accurate dosing, which impacts treatment success *(5, 27)*. However, as of December 2015, new dispersible, palatable, affordable and simple to administer fixed-dose formulations are available, which should improve treatment outcomes for children *(28)*.

The research on anti-TB treatment adherence among children is scarce. One study in India found that poor adherence rates could be attributed to conflicts between school and health centre hours, parental concerns over job absenteeism and resultant loss of wages, and the distance and cost of travel to and from health centres administering treatment to children with TB *(25)*. Just as in adults, the side-effects of the treatment regimen can also contribute to poor adherence *(29)*.

Health system constraints

Missed opportunities in contact investigation

WHO recommends that all children under the age of 5 be screened following close contact with someone, most commonly an adult family member, with active TB *(12)*. The guidelines also recommend that all children living with HIV be screened, irrespective of contact *(12)*. However, these practices are rarely implemented in endemic settings, where health workers are already overstretched and the legal frameworks ensuring that children who are close contacts of people with TB be presented for screening may be lacking *(6, 15, 30–36)*. For example, a study in Malawi found that child contacts were screened for TB in only 9% of cases where an adult had been admitted to hospital, and only 21% of adults with TB with children under the age of 5 living at home were informed by their health workers of the need for childhood screening *(37)*. Given that screening costs can account for a significant proportion of household incomes, it can be difficult to convince parents or other adult caregivers of the need to bring a child with no outward symptoms of TB for screening *(30, 35)*. Even if screening does occur as part of a contact investigation, many health workers are not trained in how to consider and recognize the symptoms of TB in children. This lack of training increases the likelihood of a missed diagnosis and/or the child being started on inappropriate treatment *(6, 37)*. Active screening, whereby the health worker actively seeks out close contacts, has been shown to increase case finding, but carries with it additional challenges *(30)*. Health workers are often required to pay for their own transport, may have trouble locating families with temporary addresses and are sometimes forced to visit areas where they feel their safety is at risk *(17, 35, 38)*.

Underreporting of childhood TB to NTPs

Children with TB often do not present to district divisions of NTPs for diagnosis and treatment, but rather first seek care from general child health services or private health care providers *(6, 36)*. NTPs only become aware of the child with TB if the health worker or private provider notifies the NTP, but often this does not happen *(6, 39, 40)*. Since childhood TB does not form part of the training for health professionals, knowledge of the disease is low among practitioners in both the public and private sector; this can also lead to the child not being referred to the NTP for appropriate care *(41)*. At the same time, child health services are unable to administer the appropriate management for children who are close contacts of someone with TB if the NTP does not share the relevant information *(36)*. Crucial opportunities for intervention are being missed due to gaps in reporting, low knowledge, and the lack of integration of care for childhood TB in national programmes. The weak linkages between the various health care providers also mean that national surveillance statistics are incomplete and do not provide an accurate picture of the TB burden in this population.

Current isoniazid preventative therapy (IPT) guidelines and IPT adherence

IPT can be a highly effective intervention in preventing the progression from latent TB to active TB. WHO guidelines recommend six months of IPT for children under the age of 5 who live in households with or are close contacts of people who have TB *(12)*. However, CXRs are included in some national guidelines as a mandatory screening test to determine whether the child should be started on preventative treatment or anti-TB medication *(30, 33)*. In resource-constrained settings, it is often not possible to administer such tests, especially at peripheral health facilities *(5, 30, 33)*. Clinicians who comply with these guidelines, however, may inadvertently be preventing children from starting on potentially lifesaving treatment as soon as possible while they wait for test results *(30)*. The waiting time and the need for the back and forth commute to the central health centres where these tests can be conducted also entail additional costs for the child and their caregiver *(30)*. Recently published WHO guidelines recommend starting children who are close contacts of people with active TB on IPT following a negative clinical TB diagnosis *(12)*. However, given the difficulties of obtaining even a clinical diagnosis, these simplified guidelines could be costing lives and thus may need to be revised.

The efficacy of IPT has been shown to be extremely high, but the few studies conducted have found adherence rates to be low *(42–44)*. In many low-income countries, IPT is still not in general use because of concerns over the risk of creating drug resistance, the risk of toxicity and low protection caused by poor adherence rates *(31)*. The side-effects of IPT are minimal in children *(31)*. There are a myriad of possible reasons for nonadherence, but financial barriers to medication collection, which includes the cost of the medication itself and the cost of transportation, are most frequently cited *(44)*. Other reasons for nonadherence include the difficulties adult caregivers have in administering medication and the belief that IPT is not necessary for otherwise healthy children *(44)*. It is also thought that limited knowledge among primary caregivers about IPT and poor compliance with existing guidelines also serve as barriers to children being started on preventative treatment *(35)*.

Parent/caregiver constraints

Caregiver–child relationships

Parents and other adult caregivers act as the principal gatekeepers of children's health *(45)*. Adults have control over most aspects of a child's health, determining the amount and quality of food the child eats, what health care he or she receives, and the amount of emotional support and assistance he or she receives in times of illness *(45)*. Much of this is conditioned by the availability of resources, access to services, knowledge and awareness of diseases, and other cultural factors *(45)*. Strong, nurturing relationships between caregiver, most notably the mother, and child have been demonstrated to have positive impacts on a range of health outcomes, even in resource-limited settings *(45)*. Conversely, the absence of at least one strong relationship can lead to negative health outcomes for the child *(45)*. Although there have been no studies on the importance of strong relationships between child and adult caregiver in TB treatment, it is reasonable to expect that treatment outcomes and adherence are likely to be more successful when the child is able to access emotional support from an adult caregiver, and when parents and caregivers are in turn adequately supported in providing such care.

Household poverty

Despite the presence of free TB diagnosis and care in most countries, the direct and indirect costs of obtaining a TB diagnosis and starting on treatment can be catastrophic *(46, 47)*. Children living in poverty are more likely to live in crowded and poorly ventilated households, making it more likely that they will come into contact with infected adults *(11, 48, 49)*. The child's household may already be trying to absorb the costs associated with a positive TB diagnosis in an adult member of the family, such as loss of income. In such cases, health seeking by other members of the family is likely to be delayed because the household simply cannot afford the additional costs *(50)*. A delayed diagnosis of childhood TB puts the life of the child at risk. Smoke from indoor cooking fires, most commonly used in poorer households, can weaken children's lungs and increase their vulnerability to TB (51). Poor nutrition, linked closely to poverty, can impact the effectiveness of TB treatment *(52)*. Malnutrition in children can also increase the likelihood of a missed diagnosis when TSTs are administered *(14)*.

Sociocultural barriers to treatment

Stigma

Stigma has been shown to influence health-seeking behaviours for children with TB. A recent study conducted in Zambia found that people generally believed that children could not get TB, which led to children with TB feeling uneasy in their social environment *(53)*. A lack of understanding of how the disease spreads also led to the social exclusion of children with TB *(53)*. Research in India found that the social stigma of TB prevented adolescent females from seeking care at public health centres *(25)*. A study in Peru found that middle-class parents believed that good nutrition could act as effective immunization against TB. This belief, coupled with the view that TB was a disease of the poor, prevented these parents from getting their children tested for TB. Instead, symptoms of the disease, such as a persistent cough, were attributed to other illnesses *(17)*.

Gender

Barriers to health care access are typically higher for women in TB endemic areas due to a number of competing factors, including sociocultural disempowerment, stigma and a lack of financial resources *(21)*. Although there have been very few studies examining the link between gender and TB in children, it is perhaps safe to assume that gender plays a role in determining health outcomes, particularly in low-income settings. A study in Pakistan found that male infants enjoy better nutrition and health care access than females of the same age, and that this neglect continues into adulthood *(54)*. A further study of childhood TB in Pakistan noted that a significantly higher number of girls are diagnosed with TB *(55)*. The authors of the study suggested that this finding could be attributed to the poor nutritional status of the female children in the region, making them more vulnerable to TB *(55)*.

A study conducted in Bangladesh found a link between educational status and the likelihood of development of childhood TB *(49)*. The study found that children who completed primary education had less than one third the risk of developing childhood TB compared to those who did not complete primary education *(49)*. The same study also noted that maternal education and occupational status were both statistically significantly linked to childhood TB *(49)*. Given that female literacy rates are lower than male literacy rates in much of the developing world, this perhaps serves as another indicator of how important gender is in determining health outcomes *(56)*.

Policy considerations

Childhood TB has, until very recently, been largely ignored by policy makers *(11)*. NTPs have traditionally focused on addressing TB in adults. In low-resource settings, it may seem counter-intuitive to divert resources to a population that contributes little to the spread of the disease *(11)*. However, without supporting children with TB, elimination strategies will ultimately fail because children "provide the reservoir out of which future cases will develop" *(11)*. Important steps are being taken to bring attention to childhood TB on an international level, but more needs to be done at the national and local levels to bring treatable and preventable TB under control *(36)*.

Taking action

Improving case finding

Contact tracing is essential to the early identification of childhood TB. The identification of household contacts of people with TB has been shown to be an effective means of TB control *(48)*. However, contact tracing in both its passive and active forms is rarely practised in high-burden settings. This could be because of lack of resources, poor knowledge about TB transmission, or the high levels of stigma surrounding TB, or because health workers are not trained to inform people with TB to identify close contacts for screening. The poor sensitivity of diagnostic tools also hampers case finding in children.

Intensive education sessions with people receiving TB treatment have been shown to be effective in increasing the number of close contacts brought in for screening. These interventions should not only educate people with TB as to the purpose of contact tracing, but also equip them with practical skills with which to convince close contacts to present for screening *(57)*. Parents, or adults living in households with children, need to be informed to bring children for screening.

Implementing standard operating procedures (SOPs) can also have a positive impact on case finding. These could be developed to fill case detection gaps for children by ensuring that health workers inform all people with TB of the need to bring in close contacts for screening and that health workers examining children are trained to consider the symptoms of childhood TB *(58)*.

Engaging private providers and informing the public

A true epidemiological profile of TB in children has been hampered by poor surveillance methods and underreporting. In many countries, clinical data from adults are extrapolated to children, but this method fails to take into account the specific nature of TB in children. Improved epidemiological data on the TB burden and effectiveness of intervention in children are vital to helping national governments formulate effective responses to the disease. A crucial first step is for NTPs to identify where children and their families first access health care. In low-resource settings, this may often be through private providers. However, potential TB cases are often missed or not reported by private providers. Therefore, it is imperative that NTPs engage with private providers to ensure that they consider the symptoms of TB and that any child presenting with these symptoms is referred either to the national TB paediatric centre, if such a service exists, or to the NTP. Successful initiatives have involved working with private providers by providing financial incentives for them to refer children with TB symptoms to NTPs *(59)*. Mass publicity campaigns about the symptoms of childhood TB and the services that are available to children are also effective in improving case notification *(59)*.

Mitigating catastrophic costs

Poverty poses a significant barrier to health seeking, and a positive TB diagnosis can serve to exacerbate the effects of poverty. The family of a child with TB is likely to still be reeling from the shock of at least one positive TB diagnosis in their household. Cash transfer initiatives could be provided in exchange for treatment adherence, and could also be used as an incentive to encourage and support people with TB to bring in close contacts for screening. Other initiatives, such as the provision of vouchers for chest X-rays and free transportation to and from health facilities could be employed to improve case detection and treatment outcomes.

Utilizing peer networks

Integrated Health Services (IHS Pakistan), a national health care organization, ran a programme in Pakistan called the Little Doctors Club *(60)*. This programme used school children as ambassadors to create awareness of TB among their classmates, parents and community *(60)*. The children who were trained as ambassadors provided support to children with TB from diagnosis through to eventual recovery. By the end of 2012, the programme had identified 4,400 new TB cases *(61)*. The use of peer networks such as the Little Doctors Club could be expanded to other settings.

Keeping mother and child together during treatment

Children with TB are often treated like "mini adults" when accessing TB care. Child-specific TB services are rare in low-resource settings. Given the importance of child–caregiver relationships in improving health outcomes, providing resources that would allow mothers to support their children during TB treatment might treatment adherence and success.

Recommendations

While these recommendations provide an outline for action for a range of key stakeholders, others, including UN Agencies and local and global health worker collectives, should take note and assess their potential for use in improving TB prevention, treatment and care in children.

Civil Society	National Governments	Donor Community
Advocate on behalf of children and their families to push for more child appropriate services;	Improve surveillance data on childhood TB by ensuring that there are clear pathways for children with TB to be registered with NTPs and to receive appropriate care; collect more age- and sex-disaggregated data on the TB burden in children;	Address research gaps on childhood TB, specifically those related to improving diagnosis and case finding;
Raise awareness of the symptoms of childhood TB through education and publicity;	Improve case detection through raising awareness and training health workers; do not miss critical opportunities for intervention;	Fund research into more effective diagnostic tests for children;
Foster local expertise and leadership; develop training and reference materials that can be used by adult caregivers and community health workers;	Develop family- and community-centred strategies for treatment;	Meet funding needs for the development of such strategies;
Advocate on behalf of children by putting pressure on drug companies to develop more child-friendly anti-TB treatment options;	Work with patent offices regionally and nationally to fast-track essential TB medications suitable for children;	Fund research into more child-friendly anti-TB treatment options for children;
Advocate for broader education and integration of health care providers on issues of childhood TB;	Introduce pre-service curriculum changes for health care professionals that focus on childhood diseases, such as TB;	Support the development of curriculum changes;
Raise awareness of services available to children and their families.	Make TB diagnosis and treatment more accessible to children and their families.	Push for greater integration of TB care into child health programmes at facility and community levels.

References

1. MDR-TB in children: a Q&A with PIH's Dr. Mercedes Becerra. Boston: Partners in Health; 2014 (http://www.pih.org/blog/mdr-tb-in-children-a-qa-with-pihs-dr.-mercedes-becerra, accessed 2 October 2015).
2. Walls T, Shingadia D. Global epidemiology of paediatric tuberculosis. Journal of Infec-tion. 2004;48(1):13–22.
3. Marais B, Hesseling A, Gie R, Schaaf H, Beyers N. The burden of childhood tuberculosis and the accuracy of community-based surveillance data. Int J Tuberc Lung Dis. 2006;10(3):259–63.
4. Marais BJ, Schaaf HS. Childhood tuberculosis: an emerging and previously neglected problem. Infectious Disease Clinics of North America. 2010;24(3):727–49.
5. Getahun H, Sculier D, Sismanidis C, Grzemska M, Raviglione M. Prevention, diagnosis, and treatment of tuberculosis in children and mothers: evidence for action for maternal, neona-tal, and child health services. J Infect Dis. 2012;205 Suppl2:S216–27.
6. Coghlan R, Gardiner E, Amanullah F, Ihekweazu C, Triasih R, Grzemska M, et al. Un-derstanding market size and reporting gaps for paediatric TB in Indonesia, Nigeria and Paki-stan: supporting improved treatment of childhood TB in the advent of new medicines. PloS One. 2015;10(10):e0138323.
7. Starke J. Childhood tuberculosis. A diagnostic dilemma. CHEST Journal. 1993;104(2):329–30.
8. Eamranond P, Jaramillo E. Tuberculosis in children: reassessing the need for improved diagnosis in global control strategies. Int J Tuberc Lung Dis. 2001;5(7):594–603.
9. Marais BJ, Gie RP, Schaaf HS, Beyers N, Donald PR, Starke JR. Childhood pulmonary tuberculosis: old wisdom and new challenges. Am J Respir Crit Care Med. 2006;173(10):1078–90.
10. Desikan P. Sputum smear microscopy in tuberculosis: is it still relevant? Indian J Med Res. 2013;137(3):442–4.
11. Seddon JA, Shingadia D. Epidemiology and disease burden of tuberculosis in children: a global perspective. Infect Drug Resist. 2014;7:153–65.
12. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Geneva: World Health Organization; 2014.
13. Out of the dark: meeting the needs of children with TB. Geneva: Médecins Sans Fron-tières; 2011 (http://www.msfaccess.org/sites/default/files/MSF_assets/TB/Docs/TB_report_OutoftheDark_ENG_2011_Final.pdf, accessed 1 October 2015).
14. Roadmap for childhood tuberculosis: towards zero deaths. Geneva: World Health Organ-ization; 2013.
15. Global tuberculosis report 2015. Geneva: World Health Organization; 2015.
16. Marais B, Graham S, Cotton M, Beyers N. Diagnostic and management challenges for childhood tuberculosis in the era of HIV. J Infect Dis. 2007;196 Suppl 1:S76–85.
17. Chiang S, Roche S, Contreras C, Alarcón V, Del Castillo H, Becerra M, et al. Barriers to the diagnosis of childhood tuberculosis: a qualitative study. Int J Tuberc Lung Dis. 2015;19(10):1144–52.
18. Marais B, Obihara C, Warren R, Schaaf H, Gie R, Donald P. The burden of childhood tuberculosis: a public health perspective [Review Article]. Int J Tuberc Lung Dis. 2005;9(12):1305–13.
19. Lapphra K, Sutthipong C, Foongladda S, Vanprapar N, Phongsamart W, Wittawat-mongkol O, et al. Drug-resistant tuberculosis in children in Thailand. Int J Tuberc Lung Dis. 2013;17(10):1279–84.
20. Jeena P, Pillay P, Pillay T, Coovadia H. Impact of HIV-1 co-infection on presentation and hospital-related mortality in children with culture proven pulmonary tuberculosis in Durban, South Africa. Int J Tuberc Lung Dis. 2002;6(8):672–8.
21. Marais BJ, Gupta A, Starke JR, El Sony A. Tuberculosis in women and children. Lancet. 2010;375(9731):2057–9.
22. Whittaker E, Zar HJ. Promising directions in the diagnosis of childhood tuberculosis. Ex-pert Rev Respir Med. 2012;6(4):385–95.
23. Detjen AK, DiNardo AR, Leyden J, Steingart KR, Menzies D, Schiller I, et al. Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children: a systematic review and meta-analysis. Lancet Respir Med. 2015;3(6):451–61.
24. Morales S-VM, Llopis GA, Sanz AS, Otero M, Pérez-Tamarit D, Asensi BF. Delay in childhood tuberculosis detection as a negative factor in the anti-tuberculosis struggle. Revista Clinica Espanola. 1992;191(9):463–7.
25. Arora V, Gupta R. Directly observed treatment for tuberculosis. Indian J Pediatr. 2003;70(11):885–9.
26. "My grandson, he's a warrior!" Treating children with drug-resistant TB in Swaziland. Geneva: Médecins Sans Frontières; 2011 (http://www.msfaccess.org/content/my-grandson-hes-warrior-treating-children-drug-resistant-tb-swaziland, accessed 1 October 2015).
27. DR-TB drugs under the microscope: sources and prices for drug-resistant tuberculosis medicine. Geneva: Médecins Sans Frontières; 2013 (https://www.msfaccess.org/sites/default/files/MSF_TB_Report_UTM3rdEdition-2013.pdf, ac-cessed 1 October 2015).
28. TB Alliance and partners announce world's first availability of appropriate, child-friendly TB medicines in correct doses. New York: TB Alliance; 2015 (http://www.tballiance.org/news/tb-alliance-announces-worlds-first-appropriate-child-friendly-tb-medicines, accessed 23 January 2015).
29. Awofeso N. Anti-tuberculosis medication side-effects constitute major factor for poor adherence to tuberculosis treatment. Bull World Health Organ. 2008;86(3):B–D.
30. Zachariah R, Spielmann M, Harries A, Gomani P, Graham S, Bakali E, et al. Passive versus active tuberculosis case finding and isoniazid preventive therapy among household con-tacts in a rural district of Malawi. Int J Tuberc Lung Dis. 2003;7(11):1033–9.
31. Gomes V, Wejse C, Oliveira I, Andersen A, Vieira F, Carlos L, et al. Adherence to isoni-azid preventive therapy in children exposed to tuberculosis: a prospective study from Guinea-Bissau. Int J Tuberc Lung Dis. 2011;15(12):1637–43.
32. Hill PC, Rutherford ME, Audas R, van Crevel R, Graham SM. Closing the policy-practice gap in the management of child contacts of tuberculosis cases in developing countries. PLoS Med. 2011;8(10):e1001105.
33. Triasih R, Rutherford M, Lestari T, Utarini A, Robertson CF, Graham SM. Contact inves-tigation of children exposed to tuberculosis in South East Asia: a systematic review. J Trop Med. 2012;2012:301808.
34. Detjen A, Gnanashanmugam D, Talens A. A framework for integrating childhood tuber-culosis into community-based child health care. Washington, DC: CORE Group; 2013.
35. Rutherford ME, Ruslami R, Anselmo M, Alisjahbana B, Yulianti N, Sampurno H, et al. Management of children exposed to Mycobacterium tuberculosis: a public health evaluation in West Java, Indonesia. Bull World Health Organ. 2013;91(12):932–41A.
36. Graham SM, Grzemska M, Brands A, Nguyen H, Amini J, Triasih R, et al. Regional initia-tives to address the challenges of tuberculosis in children: perspectives from the Asia-Pacific region. Int J Infect Dis. 2015;32:166–9.
37. Claessens N, Gausi F, Meijnen S, Weismuller M, Salaniponi F, Harries A. Screening childhood contacts of patients with smear-positive pulmonary tuberculosis in Malawi [Notes from the Field]. Int J Tuberc Lung Dis. 2002;6(4):362–4.
38. Pothukuchi M, Nagaraja SB, Kelamane S, Satyanarayana S, Shashidhar BS, Babu S, et al. Tuberculosis contact screening and isoniazid preventive therapy in a South Indian district: operational issues for programmatic consideration. PLoS One. 2011;6(7):e22500.
39. Lestari T, Probandari A, Hurtig A-K, Utarini A. High caseload of childhood tuberculosis in hospitals on Java Island, Indonesia: a cross sectional study. BMC Public Health. 2011;11(1):784.
40. Preez KD, Schaaf H, Dunbar R, Swartz A, Bissell K, Enarson D, et al. Incomplete regis-tration and reporting of culture-confirmed childhood tuberculosis diagnosed in hospital. Public Health Action. 2011;1(1):19–24.
41. Prasad R. Nuances of childhood TB are never taught in medical schools. The Hindu. 12 December 2013 (http://www.thehindu.com/sci-tech/health/nuances-of-childhood-tb-are-never-taught-in-medical-schools/article5448312.ece, accessed 22 November 2015).
42. Marais BJ, van Zyl S, Schaaf HS, van Aardt M, Gie RP, Beyers N. Adherence to isonia-zid preventive chemotherapy: a prospective community based study. Arch Dis Child. 2006;91(9):762–5.
43. Machado Jr A, Finkmoore B, Emodi K, Takenami I, Barbosa T, Tavares M, et al. Risk factors for failure to complete a course of latent tuberculosis infection treatment in Salvador, Brazil. Int J Tuberc Lung Dis. 2009;13(6):719–25.
44. Rutherford ME, Ruslami R, Maharani W, Yulita I, Lovell S, Van Crevel R, et al. Adher-ence to isoniazid preventive therapy in Indonesian children: a quantitative and qualitative inves-tigation. BMC Research Notes. 2012;5(1):7.
45. The importance of caregiver-child interactions for the survival and healthy development of young children: a review. Geneva: World Health Organization; 2004.
46. Janssens J-P, Rieder H. An ecological analysis of incidence of tuberculosis and per capita gross domestic product. Eur Respir J. 2008;32(5):1415–6.
47. Foster N, Vassall A, Cleary S, Cunnama L, Churchyard G, Sinanovic E. The economic burden of TB diagnosis and treatment in South Africa. Soc Sci Med. 2015;130:42–50.

48. Caldeira ZM, Sant'Anna CC, Aidé MA. Tuberculosis contact tracing among children and adolescents, Brazil. Revista de Saude Publica. 2004;38(3):339–45.

49. Karim M, Rahman M, Mamun S, Alam M, Akhter S. What cannot be measured cannot be done; risk factors for childhood tuberculosis: a case control study. Bangladesh Med Res Counc Bull. 2012;38(1):27–32.

50. Management of sick children by community health workers: intervention models and programme examples. Geneva: The United Nations Children's Fund and World Health Organi-zation; 2006.

51. Lin H, Ezzati M, Murray M. Tobacco Smoke. Indoor air pollution and tuberculosis: a sys-tematic review and meta-analysis PLoS Med. 2007;4(1):e20.

52. HIV, AIDS, TB and Nutrition. World Food Programme; 2012.

53. Cremers AL, de Laat MM, Kapata N, Gerrets R, Klipstein-Grobusch K, Grobusch MP. Assessing the consequences of stigma for tuberculosis patients in urban Zambia. PLoS ONE. 2015;10(3):e0119861.

54. Nasrullah M, Bhatti JA. Gender inequalities and poor health outcomes in Pakistan: a need of priority for the national health research agenda. J Coll Physicians Surg Pak. 2012;22(5):273–4.

55. Batra S, Ayaz A, Murtaza A, Ahmad S, Hasan R, Pfau R. Childhood tuberculosis in household contacts of newly diagnosed TB patients. PLoS One. 2012;7(7):e40880.

56. Adult and youth literacy: global trends in gender parity. Montreal: UNESCO Institute for Statistics; 2010.

57. Ekwueme O-eC, Omotowo BI, Agwuna KK. Strengthening contact tracing capacity of pulmonary tuberculosis patients in Enugu, southeast Nigeria: a targeted and focused health education intervention study. BMC Public Health. 2014;14(1):1175.

58. Ayalneh H. Improving TB case detection by implementing standard operating procedures (SOPs) in selected health facilities in Ethiopia. Medford, MA: Management Sciences for Health; 2012.

59. Khan AJ, Khowaja S, Khan FS, Qazi F, Lotia I, Habib A, et al. Engaging the private sec-tor to increase tuberculosis case detection: an impact evaluation study. Lancet Infect Dis. 2012;12(8):608–16.

60. Fight against tuberculosis by school students. Washington, DC: USAID; 2011 (https://www.usaidassist.org/resources/fight-against-tuberculosis-school-students, accessed 6 October 2015).

61. Jamla S. Little doctors identify thousands of TB patients. Pakistan Observer. 24 Decem-ber 2012.

Stop TB Partnership

a partnership hosted by United Nations at UNOPS

END TB

The Stop TB Partnership acknowledges with gratitude the financial and technical support received from the Global Fund to Fight AIDS, TB & Malaria.

Stop TB Partnership

Chemin de Blandonnet 2,

1241 Vernier

Geneva, Switzerland

www.stoptb.org