

**TOWARDS  
ZERO  
DEATHS**

# **ROADMAP FOR CHILDHOOD TUBERCULOSIS**



**World Health  
Organization**



**unicef** 



**International Union  
Against Tuberculosis  
and Lung Disease**

**TAG**  
Treatment Action Group

**StopTB Partnership**



**USAID**  
FROM THE AMERICAN PEOPLE

# Key facts about children and tuberculosis (TB)

## TB exposure

- Any child living or spending time in a setting where there are people with infectious TB may be exposed to *Mycobacterium tuberculosis*.

## TB infection

- Infection with *M. tuberculosis* usually follows exposure to a person with TB who is coughing; infection occurs when TB bacilli are inhaled into the respiratory system.
- The likelihood of becoming infected following exposure is greatest when there has been close contact with an infected person (for example, in a household) and if the infected person has sputum smear-positive pulmonary TB. However, transmission can also occur from persons with smear-negative, culture-positive pulmonary disease.
- When infection occurs, the TB bacilli multiply and drain to regional lymph nodes where cell-mediated immunity is activated to contain the infection. The tuberculin skin test is an indicator of this immune response to infection, and will usually become positive within 8–12 weeks of infection. Around 90% of children infected with *M. tuberculosis* will contain the infection and remain well.

## Progressing from infection to disease

- Any child infected with *M. tuberculosis* may develop TB.
- Most children develop TB disease within one year of becoming infected. This is why taking a contact history is relevant, and why the burden of TB in children reflects continuing transmission within a population.
- Risk factors for developing disease following infection include young age (that is, being less than three years old) and immunodeficiency (such as that caused by HIV infection, measles or severe malnutrition). Adolescence is another period during which there is an increased risk of developing disease.
- Progression from infection to disease is indicated by the onset of symptoms.

## TB disease

- The most common type of TB disease in children is pulmonary TB, of which sputum smear-negative disease is most frequent. Cases in which sputum cannot be obtained for smear microscopy are also considered to be and reported as sputum smear-negative.
- Extrapulmonary TB occurs in approximately 20–30% of all cases in children; TB adenitis and TB pleural effusion are the most common forms.
- The presentation of TB disease in children is age-related and dependent on immune response. Infants and young children are at particular risk of developing severe, disseminated and often lethal disease, which may present as TB meningitis or miliary TB. Adolescents are at particular risk of developing adult-type disease (that is, they are often sputum smear-positive and highly infectious).
- Diagnosing TB in HIV-positive children is similar to diagnosing HIV-negative children of a similar age.



# ROADMAP FOR CHILDHOOD TUBERCULOSIS

TOWARDS ZERO DEATHS



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- Top right: WHO/Damien Schumann  
Caption: For Zanele and Lilathi, the fight is not over. They will have to stick to their clinic appointments and keep taking their medication. But thanks to the integrated TB and HIV services provided in Nyanga they both have the chance to lead fulfilling lives. Without these services, Zanele's TB could have been ignored in the shadow of HIV.
- Top left: WHO/HM.Dias  
Caption: Jerome has multidrug-resistant TB, he has been undergoing treatment for over a month at the East Avenue Medical Center, Philippines.
- Bottom right: ECDC/Tobias Hofsäss

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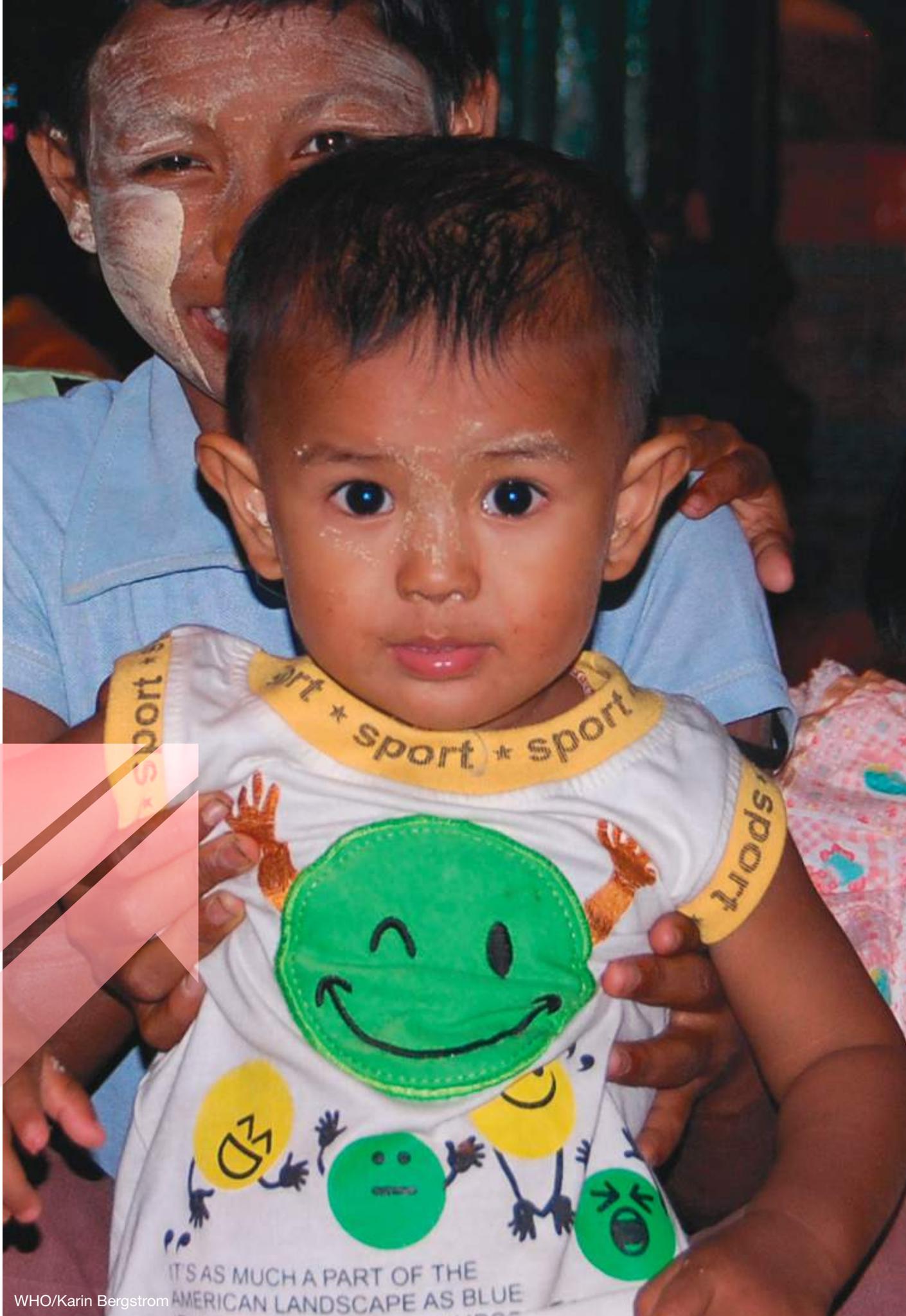
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# Abbreviations

AIDS	acquired immunodeficiency syndrome
BCG	bacille Calmette–Guérin
DOTS	basic package of interventions for TB control that underpins the <i>Stop TB strategy</i>
GDP	gross domestic product
HIV	human immunodeficiency virus
iCCM	integrated community case management
IMCI	integrated management of childhood illness
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Group
MDR-TB	multidrug-resistant tuberculosis
TB	tuberculosis
WHO	World Health Organization



WHO/Karin Bergstrom

IT'S AS MUCH A PART OF THE AMERICAN LANDSCAPE AS BLUE

# Preface

After decades of being relegated to the shadows, the childhood tuberculosis (TB) epidemic is now in the global spotlight. The goal of a world with zero TB deaths in children has been endorsed by the international TB community and has melded key stakeholders to make this goal a reality. This is a significant breakthrough for partners and advocates who have worked tirelessly to draw attention to the misunderstood epidemic of TB in children.

The urgency of the problem of TB in children, whose full scope is still not fully known, cannot be underestimated. World Health Organization (WHO) estimates in 2012<sup>1</sup> revealed that up to 74 000 children die from TB each year and children account for around half a million new cases annually. It should be noted that the estimated deaths only include those in human immunodeficiency virus (HIV)-negative children. In fact, the actual burden of TB in children is likely higher, especially given the challenge in diagnosing childhood TB. Compounding this difficulty with diagnosis is the fact that children with TB often come from families that are poor, lack knowledge about the disease and live in communities with limited access to health services. Another compelling reason is that TB is important in the context of children's overall survival. We do not know the extent to which TB is a cause of childhood deaths that are reported in global statistics as deaths due to HIV, pneumonia, malnutrition or meningitis, but the number is likely to be substantial.

The strategy for global TB control expanded beyond DOTS in 2006 with the Stop TB strategy. This emphasizes prioritization of actions for vulnerable populations such as children, including intensified case- and community-based care.<sup>2</sup> A post-2015 TB strategy is currently being developed and the proposed framework includes increased focus on TB care for children integrated with child health and HIV services as well as other preventive services. Building on the global strategies, as well as the global child survival movement – *A Promise Renewed* – this roadmap developed by WHO and partners under the aegis of the Childhood TB Subgroup lays out the strategic framework for combating childhood TB. This provides an important opportunity to address TB in children and needs to be backed with enhanced resource commitments both globally and nationally. Global estimates indicate that at least US\$ 80 million per year will be required to address TB in children. An additional US\$ 40 million per year will be needed for antiretroviral therapy and co-trimoxazole preventive therapy for children coinfecting with TB and HIV. Filling this resource gap would save tens of thousands of children's lives from this preventable and curable disease.

Furthermore, success in ending the TB epidemic in children cannot be achieved without advances in research and development. There is urgent need for improved diagnostic and treatment options for children with TB. The research community needs to come forward and take action to address these challenges.

At the country level there is good news. A significant transformation of political will and commitment to intensify efforts to address TB among children has taken place. National TB programmes are increasingly striving to address the challenges of caring for children with TB, including those infected with both HIV and TB, and children who are close contacts of people with TB. National priorities are being identified, and countries

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1 *Global tuberculosis report 2013*. Geneva, World Health Organization, 2013 (in press).

2 DOTS is the basic package of interventions for TB control that underpins the *Stop TB strate*. For more information, see: *The Stop TB strategy: building on and enhancing DOTS to meet the TB-related Millennium Development Goals*. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.368). (Available from [http://whqlibdoc.who.int/hq/2006/WHO\\_HTM\\_STB\\_2006.368\\_eng.pdf](http://whqlibdoc.who.int/hq/2006/WHO_HTM_STB_2006.368_eng.pdf)).

have had more input into international activities that address TB in children. A growing number of national TB programmes are forming working groups and dedicating staff to coordinating activities aimed at addressing childhood TB. National policies and guidelines are being developed or updated, but there is still a wide gap between policy and practice that must be bridged.

While efforts by TB programmes contribute to combating the childhood TB epidemic, the root of this problem can only be addressed with the engagement and accountability at all levels of the health care system and community. Children with TB present to health services in the same context as children with common childhood illnesses, which is generally at primary and secondary care settings. This includes those that provide maternal and child health care, HIV care, or nutritional rehabilitation support, as well as outpatient and inpatient facilities that care for sick children or adults with TB. In fact, the most obvious point of entry into the health system for many children with TB (or those who are contacts of someone with TB) is at the community level, where the child's parent, guardian or other household contacts have been diagnosed with TB or where their care is being managed. In order to offer a more comprehensive and effective service at the community level for children and their families affected by TB, increased efforts are being launched to improve integration, coordination and communication among different care providers. Decentralizing TB care for children is also likely to be highly cost effective because it will improve access to diagnosis and the early initiation of treatment, and will not require a large increase in resources.

This is a pivotal moment in the fight against childhood TB. We need determined leadership, political commitment at all levels and research – all backed by sustainable resources to achieve the goal of zero TB deaths in children. We also need to move beyond the traditional approach to TB care and control by working synergistically across the entire health system and partnering with communities, making the most of critical opportunities to get to zero deaths among children with TB.

Any child that dies from TB is one child too many, so there should be no question of 'why' to act. This roadmap shifts us toward 'how' we can chart a course to accelerate progress against this deadly disease in children.



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# Executive summary

The goal of reaching zero tuberculosis (TB) deaths among children worldwide is within our grasp. Achieving this requires sustained advocacy, greater commitment, mobilization of increased resources and a joint effort by all stakeholders involved in providing health care for children and in TB control. This roadmap indicates key actions and the enhanced investment urgently needed to tackle childhood TB.

## Key messages

### **Childhood TB needs to be lifted out of the shadows**

- Every day, up to 200 children<sup>3</sup> lose their lives to tuberculosis – a preventable and curable disease.
- Over half a million children fall ill with TB each year and struggle with treatment that is not child friendly.
- TB in children is often missed or overlooked due to non-specific symptoms and difficulties in diagnosis. This has made it difficult to assess the actual magnitude of the childhood TB epidemic, which may be higher than currently estimated.
- There is an urgent need for public attention, prioritization, commitment and funding for this disease that today should never take the life of a child.

### **Research is urgently needed to address TB in children**

- Currently there is a lack of effective diagnostic tests that can detect TB in children, child-friendly drug formulations for treatment and care for children with TB and/or those in contact of someone diagnosed with TB.
- Research should include children in clinical trials for testing of new diagnostics and drugs.
- There is a need to strengthen the evidence base that supports the integration of care for childhood TB into other child care services, and also about the impact that these efforts have on TB case-finding and child survival.

### **Childhood TB can only be effectively addressed with collaboration across the health system and community**

- Childhood TB should move from being the sole responsibility of national TB programmes, as care for sick children is primarily sought in separate paediatric services at different levels of the health system. Prioritization of childhood TB is critical in national health strategies, plans and budgets.
- There is an urgent need for greater awareness of, and increased screening for, TB in children, particularly by services that serve children in settings with high prevalence of TB and human immunodeficiency virus (HIV). Children with TB often present at primary- and secondary care settings where there is a lack of guidance on how to address the challenges of diagnosing and managing childhood TB.
- Child health workers and paediatricians in both the public and private sectors should report to national TB programmes all children diagnosed with TB, so that acceptable follow up can be ensured to allow both better care and an improved understanding of TB burden.

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<sup>3</sup> children aged less than 15

## Enhanced investment is critical to end TB deaths among children

- Meeting the goal of zero TB deaths in children requires increased investment and leveraging of resources both globally and at the country level to ensure that the actions highlighted in the roadmap are undertaken.
- The World Health Organization (WHO) estimates that globally at least US\$ 80 million per year will be required to address childhood TB. An additional US\$ 40 million per year will be needed for antiretroviral therapy and co-trimoxazole preventive therapy for children coinfecting with TB and HIV. These figures probably understate the financial effort required due to lack of accurate information about the actual burden of TB among children.
- The Stop TB Partnership *Global Plan to Stop TB 2011–2015* estimates that during this period US\$ 7.7 billion is needed for research and development into TB (this represents the amount needed for all age groups).<sup>4</sup> Of this, at least US\$ 0.2 billion will be required to complete projects directly aimed at providing new tools for preventing, diagnosing and treating children who have TB. At present, only 32% of the funding needed for TB research and development is available.

## The Childhood TB Roadmap – an overview

This roadmap for addressing childhood TB outlines 10 key actions to be taken at both the global and national levels:

1. Include the needs of children and adolescents in research, policy development and clinical practice.
2. Collect and report better data, including on preventive measures.
3. Develop training and reference materials on childhood TB for health care workers.
4. Foster local expertise and leadership among child health workers at all levels of the health care system.
5. Do not miss critical opportunities for intervention (e.g. use strategies such as intensified case-finding, contact tracing and preventive therapy); implement policies for early diagnosis; and ensure there is an uninterrupted supply of high-quality anti-TB medicines for children).
6. Engage key stakeholders, and establish effective communication and collaboration among the health care sector and other sectors that address the social determinants of health and access to care.
7. Develop integrated family- and community-centred strategies to provide comprehensive and effective services at the community level.
8. Address research gaps in the following areas: epidemiology, fundamental research, the development of new tools (such as diagnostics, medicines and vaccines); and address gaps in operational research, and research looking at health systems and services.
9. Close all funding gaps for childhood TB at the national and global levels.
10. Form coalitions and partnerships to study and evaluate the best strategies for preventing and managing childhood TB, and for improving tools used for diagnosis and treatment.

<sup>4</sup> *Global plan to Stop TB 2011–2015*. Geneva, World Health Organization, 2010 (WHO/HTM/STB/2010.2). (Available from [http://www.stoptb.org/assets/documents/global/plan/TB\\_GlobalPlanToStopTB2011-2015.pdf](http://www.stoptb.org/assets/documents/global/plan/TB_GlobalPlanToStopTB2011-2015.pdf)).



H Derwish

# Childhood TB: identifying the challenges

## Defining the true burden of disease

WHO estimates that the annual global burden of TB in children<sup>5</sup> in 2012 was approximately 530 000 cases (or 6% of global TB burden), and that up to 74 000 children died from TB that year. It is important to note that TB-related deaths in children infected with HIV are not included in these estimates because they are classified as deaths caused by HIV (i.e. not TB). These estimates have further limitations, and the burden of TB in children is likely to be higher. For example, in settings with a high burden of TB, around 10–20% of all TB cases are expected to occur in children. These countries also have high rates of mortality in children who are younger than five years of age. However, in reality, many national TB programmes report numbers well below the expected range. There is no data on the burden of multidrug-resistant (MDR-TB) in children but it is likely to be considerable given that up to half a million adults fall ill worldwide with this form of TB each year. The prevention, diagnosis and management of MDR-TB in children provides special challenges for TB programmes and is often only accessible at referral levels of care.

The lack of an accurate diagnostic test for TB in young children is another major challenge, and adds to the potential for both an under-diagnosis and an over-diagnosis of cases. Even when children are diagnosed with TB and treated for it, many are not registered with or reported to/by national TB programmes.

The clinical overlap of TB symptoms with common childhood diseases results in many TB cases being missed, including the more severe and often fatal cases that present as severe pneumonia, malnutrition or meningitis. However, TB is not adequately recognized as important within the overall child survival framework. The challenge remains to better understand its contribution to the common causes of morbidity and mortality in young children, such as pneumonia, malnutrition, meningitis and HIV. Increasing evidence suggests that TB may be an important primary cause of illness or comorbidity in these contexts. As mortality in children decreases as a result of the wider implementation of vaccines, and as pneumonia, meningitis and malnutrition become less common, *Mycobacterium tuberculosis* will become relatively more important and obvious as a causative pathogen of these diseases, so treatment will hopefully become more feasible (Box 1).

### Box 1. Childhood TB: a missed opportunity to improve child survival

Many children who present with TB disease represent an opportunity missed by the health system to have prevented the disease. This is particularly the case for infants and young children: studies consistently show that most cases of TB in children occur in those with a known contact who has been diagnosed with TB, which is frequently a parent or another close relative of the child. Infants and young children are at particularly high risk for severe, disseminated TB disease and for TB-related mortality. And yet it is all too common to have the child of a parent who has TB to present with TB meningitis, which is frequently fatal, and if not, often results in marked and permanent disability. This could be prevented by screening children who are contacts of people diagnosed with TB and by providing preventive therapy for children younger than five years of age at the time TB is diagnosed in a parent or family member.

<sup>5</sup> children aged less than 15

Adolescents<sup>6</sup> are another important group at risk for TB, and there are additional management challenges that are particular to that age group, especially if an adolescent is also living with HIV. However, diagnosis is usually less challenging in adolescents with TB than in younger children because adolescents can readily provide sputum, and are commonly sputum smear-positive.

### **Struggling against historical neglect**

- Childhood TB has historically been neglected by the global TB community and the health community in general. There are a number of factors that explain this neglect.
- The difficulty in confirming a case of childhood TB: the lack of accurate, reliable diagnostic tools led to scepticism about the reliability of diagnosis and a consequent lack of confidence among health workers about their ability to identify children with TB.
- The poor recording and reporting practices for childhood TB: only sputum smear-positive cases have been routinely reported to and by national TB control programmes, and so most cases of TB in children (which are often sputum smear-negative and extrapulmonary) have not been reported; as a result, the burden of disease in children has been unrecognized at both national and international levels.
- The misperception of childhood TB as a low public health priority: children with TB are usually less infectious than adults. Consequently, they have received little attention from national TB control programmes that prioritize interrupting transmission by detecting and treating cases with sputum smear-positive TB.
- The misperception that childhood TB would disappear simply by containing TB in the adult population: modelling studies suggest that improving the detection and management of childhood TB could have a far greater impact on the health of children than improving detection and treatment of adults with TB. Further, identifying children with TB infection is important because they form a large pool of potential TB cases that can further propagate the epidemic.
- A misplaced faith in the protective efficacy of the bacille Calmette–Guérin (BCG) vaccine: although the BCG vaccine has been shown to prevent about 60% to 90% of cases of meningeal TB and disseminated TB in young children, it does not prevent a high enough proportion of cases in children or adults to be considered an adequately effective measure of TB control.
- A lack of research and investment: the scientific study of childhood TB is largely attributable to insufficient funding and inadequate interest from industry. This inattention derives partly from the difficulty with microbiological confirmation of the disease, but also originates in the reticence to conduct studies in children, and the perception that the market for innovations in the diagnosis or management of childhood TB would be too small to justify investment.
- A lack of advocacy on behalf of children and adolescents with TB from both the TB community and the child health community: the widely acknowledged underreporting of childhood TB means that its impact on children's survival has been underestimated and under recognized. Within child health programmes there has been a lack of recognition of the importance of TB; these programmes serve some of the children who are at highest risk, including those who are malnourished or have HIV/AIDS, conditions for which TB screening, treatment and prevention have the potential to substantially reduce morbidity and mortality.

Although these challenges persist, they can be overcome, and children can be diagnosed, treated and cured.

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<sup>6</sup> WHO defines adolescence as between 10 and 19 years of age.



Damien Schumann

### Addressing persisting barriers to scale up

Many of the issues of historical neglect remain barriers that will need to be overcome in order to scale up activities and services for children with TB.

#### **Prioritization in national TB programme agenda:**

Addressing childhood TB is rarely included in strategies and budgets for national TB control programmes. TB control staff often have limited knowledge of and experience with managing childhood TB. Although guidelines often exist, the gap between policy and practice is wide in childhood TB. This is particularly the case for screening children who are contacts of someone diagnosed with TB and for managing their care. Screening and treating children who are contacts of someone with TB are universally recommended but these steps are rarely implemented and if they are, there is often no record of them.

In addition, national reporting of TB cases occurring in children needs to be strengthened as it is often incomplete, and does not provide critical data disaggregated by age on the types of disease and treatment outcomes.

**Collaboration across health system and community:** Although national TB control

*“There are many contributions which the paediatrician can make to the tuberculosis control program. First the negativism about tuberculosis so prevalent in paediatrics must be overcome.... Wherever there are tuberculous adults there are infected children. No one is immune.”*

Author: Edith Lincoln, a pioneering paediatrician who originally observed the natural history of infection and TB disease in children, published original research on the protective effect of isoniazid

Source: Lincoln EM. *Eradication of tuberculosis in children*. Archives of Environmental Health, 1961, 3:444–455.

programmes are often blamed for neglecting children with TB, the broader child health community is also responsible, and has a critical role to play in overcoming the barriers to diagnosing and caring for children with TB. This was recognized more than 50 years ago but there is still often little connection between TB programmes and child health sectors.

A child with TB becomes engaged with control programmes only once a diagnosis has been made and the child has been registered. Before this stage, however, a child with TB presents simply as a sick child requiring the attention of the child health sector. When child health workers are trained, curricula often neglect the signs and symptoms of TB in children, and there is often a lack of guidance on how to address the challenges of diagnosis and management, especially at the levels of primary and secondary care, where most children with TB present.

There is a need for greater awareness and increased screening for TB in settings where services are offered to high-risk children, such as those infected with HIV and those who are malnourished. If someone in a child's family is living with HIV, then the child has an increased risk of becoming infected with TB, regardless of whether the child is HIV-positive. Limitations to the tools available for diagnosing TB, especially in young children, create the misperception that all children suspected of having TB need to be referred to a higher level of care or a specialist. This creates a further barrier to children gaining access care.

Many children who are eventually diagnosed with TB by child health workers, including by paediatricians in both the private sector and the public sector, are never registered with national TB control programmes. This is another barrier that still needs to be overcome by the child health community.

The responsibility to end the neglect and overcome barriers in order to improve the prevention and management of childhood TB therefore lies with a wide range of individuals and with services at all levels of the health care system; however, the responsibility starts in the community where the burden of TB exists. The responsibility extends to all who are engaged in delivering health care to children and adolescents, to national paediatric leaders, to researchers and advocates as well as to staff working in public health and disease control programmes, such as those addressing TB, HIV and maternal and child health.



WHO/S.Labelle

# Tackling childhood TB: a progress update

## Building an evidence base

Prior to the early 1950s, most of the published works about childhood TB were clinical descriptions of disease and large patient series focusing on the natural history of infection and disease in children. With the advent of isoniazid in 1952, the emphasis shifted to studying the treatment of infection and disease. Several large clinical trials, particularly those conducted by the United States Public Health Service, demonstrated the effectiveness of isoniazid in preventing the progression from infection to disease both in adults and children. Between the 1950s and the 1980s, research into childhood TB was sporadic and sparse, apart from some studies that demonstrated the effectiveness and safety of short-course regimens of first-line anti-TB medicines in children.<sup>7</sup>



Damien Schumann

The emergence of the HIV epidemic provided many new challenges. In the 1990s, reports of the interaction between TB and HIV infection in children were published, and included descriptions of how TB had become a common cause of morbidity and mortality in children with HIV infection who were living in areas where TB was endemic. However, research on children living in settings with a high burden of TB and HIV, that could be used to inform strategies for diagnosis and treatment, has been restricted as a result of limited resources and the infrastructure needed to conduct studies that include a large number of children with confirmed disease.

## Key achievements

### Increasing international leadership and guidance

The decade of 1995–2005 saw an unprecedented scaling up of the DOTS strategy in countries with a high burden of TB.<sup>8</sup> The creation of the Childhood TB Subgroup (as part of the DOTS Expansion Working Group of the Stop TB Partnership) in 2003 gave children a seat at the table; the subgroup provided significant input into many WHO initiatives, triggering increased advocacy around and attention to childhood TB as well as contributing to efforts to address childhood TB at the global and country levels. The subgroup has supported the development of the evidence-based guidelines listed in Figure 1.

<sup>7</sup> The box on the inner front cover summarizes key points about childhood TB from knowledge that has been accumulated primarily from early observational studies of endemic TB in North America and Western Europe.

<sup>8</sup> DOTS is the basic package of interventions for TB control that underpins the Stop TB strategy. For more information, see: *The Stop TB strategy: building on and enhancing DOTS to meet the TB-related Millennium Development Goals*. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.368). (Also available from [http://whqlibdoc.who.int/hq/2006/WHO\\_HTM\\_STB\\_2006.368\\_eng.pdf](http://whqlibdoc.who.int/hq/2006/WHO_HTM_STB_2006.368_eng.pdf).)

**Figure 1. Guidance and guidelines published with the involvement of the Childhood TB Subgroup of the DOTS Expansion Working Group of the Stop TB Partnership**



The International Childhood TB Training Course convened by Stellenbosch University and The International Union against Tuberculosis and Lung Disease, which has been held annually in Cape Town since 2007, has provided training on childhood TB to health workers from many countries who represent national TB control programmes, public health services and nongovernmental organizations, as well as researchers and educators. These workshops have helped to foster leadership at the national level, and the implementation of activities related to childhood TB by individuals who have attended the course. Examples of some of these activities are given below.

## Box 2. Examples of activities undertaken at the national level by champions of childhood TB



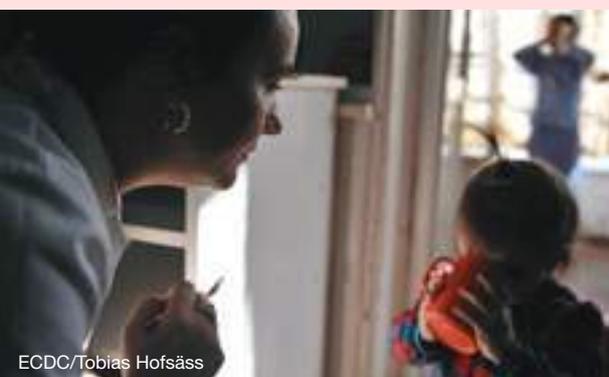
WHO/M. Grzemska

- Development of national guidelines for the management of TB in children.
- Situation analyses and identification of national priorities for implementation.



WHO/Karin Bergstrom

- Inclusion of childhood TB in reviews and monitoring missions led by national TB control programmes.
- Development of national leadership in addressing childhood TB and development of working groups focusing on childhood TB.



ECDC/Tobias Hofsäss

- Implementation and evaluation of training activities relating to TB in children.
- Development of clinical guides for managing childhood TB.

## Growing advocacy

**Global advocacy:** Several important activities occurred during 2010–2013. In 2011, an international meeting was sponsored by the Childhood TB Subgroup and the European Centre for Disease Prevention and Control. This resulted in a *Call to action for childhood TB*, which has been signed by more than 1000 individuals and organizations, and is available on the Stop TB Partnership web site.<sup>9</sup> Later that year, the unmet needs of women and children were the focus of the Stop TB symposium organized by WHO as the opening event of the 42nd Union World Conference on Lung Health in Lille. In 2012, for the first time, childhood TB was the theme for World TB Day, and was the focus of a plenary session at the 43rd Union World Conference on Lung Health as well as the focus of the Stop TB Partnership's Kochon Prize, which recognized the contributions of the Desmond Tutu TB Centre in Cape Town.

Increasing recognition of the importance of addressing TB in mothers and children: In settings with a high burden of TB, women in their childbearing years have the greatest TB burden. TB poses a considerable risk to pregnant women and their children. TB occurring in a woman with HIV is a risk factor for transmission of HIV to the infant, and is associated with premature delivery or low birth weight, and with higher mortality among mothers and children. In order to achieve Millennium Development Goals (MDG) 4 and 5, additional efforts must be made to effectively diagnose and treat mothers and their children.



As a result of advocacy efforts made during the past three years, there have been increasing calls to develop well integrated, family-based approaches to care for people coinfecting with TB and HIV, so that health services can remove barriers to access and reduce delays in the diagnosis and treatment of TB in women and children.

**Increasing attention to including children in research:** The combined advocacy of and efforts made by a number of organizations, including the WHO's Global TB Programme and the Special Programme for Research and Training in Tropical Diseases, Médecins Sans Frontières and the United States National Institutes of Health, resulted in expert panels developing standardized definitions to be used in research protocols; these definitions are aimed at improving the quality and comparability of diagnostics research. Several new research and advocacy initiatives have been developed, and these have started to address the needs of children with TB and MDR-TB. In addition to the critical need to improve diagnostic tests, research is also beginning to focus more on the TB treatment needs of children, and the care of children who are contacts of someone diagnosed with TB or MDR-TB. This increase in attention has coincided with growth in the capacity to undertake research about childhood TB in a wider range of settings than was previously possible.

<sup>9</sup> *Call to action for childhood TB*. Geneva, Stop TB Partnership, 2011. (Available from: [http://www.stoptb.org/getinvolved/ctb\\_cta.asp](http://www.stoptb.org/getinvolved/ctb_cta.asp), accessed 6August2013).



WHO/Carlos Cazalis

# The roadmap towards a TB-free future for children and adolescents

The opportunity now exists to build on past knowledge and embrace recent momentum to move forward and reduce the burden of TB in children and adolescents. Following wide consultation with the TB and child health communities, this roadmap indicates key priority actions and the enhanced investment urgently needed to tackle childhood TB.

## 1. Include the needs of children and adolescents in research, policy development and clinical practices

The needs of children and adolescents must be included in the three pillars of public health: scientific research, policy development and the implementation of appropriate clinical practices. Only when all who are involved in caring for children join forces, will a generation of children be free from TB and the move towards elimination be strengthened. In collaboration with diverse partners, WHO is proposing ambitious goals for a global strategy and targets for TB prevention, treatment and care after 2015. The strategy is built on three pillars: (1) high-quality integrated TB care and prevention; (2) bold policies and supportive systems; and (3) intensified research and innovation. The proposed strategy represents a critical opportunity for addressing childhood TB. New targets are being set in recognition of the need to develop country-specific solutions that use a 'knowing-your-epidemic' approach to prioritize activities and targets. The lack of robust, national baseline data for children makes it impossible to set targets for childhood TB. However, the broadening of the strategy from a traditional, vertically delivered public health approach to a more horizontal one, will provide an important platform from which to engage the broader child health community. National TB control programmes should develop a framework to support their activities addressing childhood TB, as suggested in Box 3.

## 2. Collect and report better data, including data on prevention

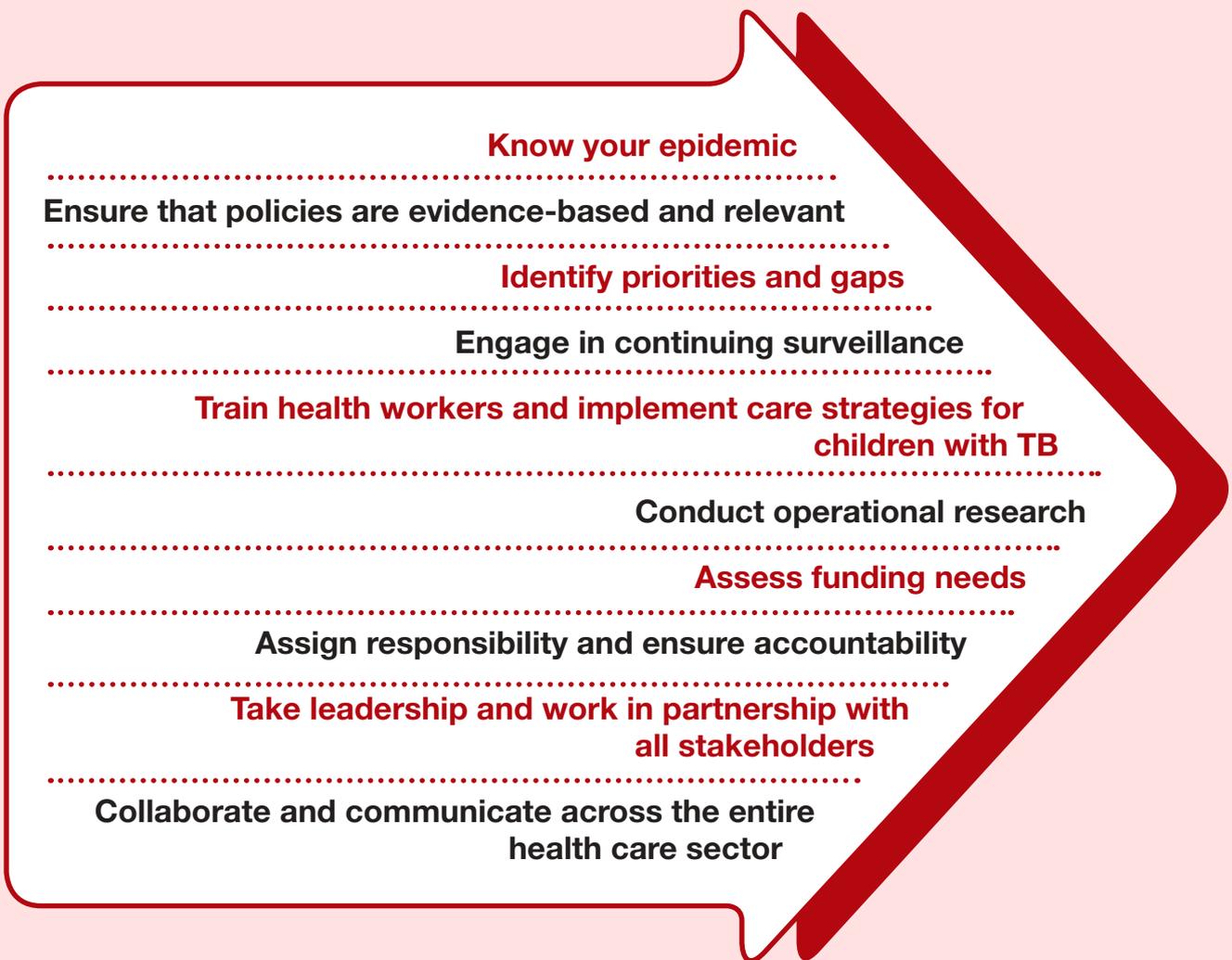
If we are to have a better idea of the actual magnitude of the problem of childhood TB, countries must include children in all TB surveillance activities. It has been previously recommended that every case of childhood TB should be registered with national TB control programmes, and reported by age, disease type, HIV status and treatment outcome (Figure 4). At a minimum, WHO standard definitions should be used.<sup>10</sup> National TB programmes may want to develop the means to provide additional data for monitoring and evaluation. National programmes need to work with child health services to improve the reporting of cases of childhood TB, including those occurring in children who are cared for in the private sector. If these steps are taken, estimates of childhood TB will improve, and not only will they allow for a better understanding of the epidemic but also they will help improve advocacy and action. Simple strategies, such as adding information about contacts to the TB treatment card of index cases, may vastly improve case-finding and contact management.

In addition, the following steps should be undertaken: systematic reviews of the literature on the burden of TB in children and adolescents; measurement of over- and

<sup>10</sup> *Definitions and reporting framework for tuberculosis – 2013 revision*. Geneva, World Health Organization, 2013 (WHO/HTM/TB/2013.2). (Available from [http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf)).

under-reporting of TB in children, and assessment of the misdiagnosis among children; a global consultation to further develop analytical methods to estimate the burden of childhood TB, and to define and prioritize the actions needed to obtain new data; promotion of case-based electronic recording and reporting systems that could facilitate the compilation and analysis of data disaggregated by age; implementation of nationwide inventory surveys to measure the under-reporting of childhood TB; implementation of more studies involving contact tracing; implementation of more studies evaluating the integration of TB activities into health services for mothers, neonates and children, in order to identify childhood cases that would otherwise remain undiagnosed; and advocacy for the further development of, and continued investment in, vital registration systems.

**Box 3. A framework for improving childhood TB activities within national TB control programmes**



### 3. Develop policy guidance, training and reference materials for health care workers

National policies and guidelines should include guidance that is specific to infants, children and adolescents; guidelines should be evidence-based and relevant to each country's specific priorities and possibilities. Currently, national TB guidelines in many countries lack sufficient detail about TB control in children. The core elements of TB control, and collaboration between HIV and TB services, that have been recommended by WHO should be adapted for children, although the methods and procedures used will vary by country and according to rates of disease, the resources available and the care provided by health systems. Each national TB control programme should identify local resources and partners, including nongovernmental organizations, which can aid the effort to develop training and reference materials.

Training is an important tool that can improve the implementation of care and control strategies. Training is required to increase the confidence and competence of health workers to recognize the clinical presentation of TB in children, and to diagnose and treat TB in children or to refer them to a higher level of care when appropriate. Training should always include the rationale for contact screening, information on clinical management and an approach for implementation. Training about childhood TB should

#### Box 4. From policy to practice through wider engagement in TB control to ensure that children are included in DOTS implementation: experiences in the Philippines

A number of steps were taken to achieve a public–private mix, from establishing policies at the national level that will give greater attention to children, to ensuring that children receive appropriate services in their communities in terms of TB diagnosis, treatment and prevention.

**1. Policy:** On 10 August 2010 a memorandum of understanding was agreed and signed by the Secretary of the Department of Health, the national TB control programme and the President of the Philippine Pediatric Society to clarify the roles that each organization would have in advocating for children with TB.

**2. Communication gap:** Community representatives were invited to the annual convention of the Philippine Coalition Against Tuberculosis, which was held jointly with the Philippine Pediatric Society in 2012. The first day of the meeting was devoted to childhood TB and attended by a number of partners including:

- a. officers from municipal community health departments, thus ensuring public and government involvement;
- b. members of five paediatric societies led by the Philippine Pediatric Society, as well as other medical personnel, including occupational health workers and physicians working in schools, thus ensuring involvement of the private sector and academia.

**3. Guidelines:** Updated childhood TB guidelines were disseminated through hospital accreditation mechanisms, reimbursement and health insurance mechanisms, and health maintenance organizations; the revised guidelines included information on paediatric dosing for anti-TB medicines that incorporated new WHO recommendations.



be integrated into the routine training and supervision provided by the national TB control programme or other training related to children's health, such as that offered to health workers in maternal and child health services and/or HIV services.

A major role of the Childhood TB Subgroup and experts in childhood TB will be to assist national TB programmes with training. Tools that could be developed include a manual for health workers or algorithms that provide clear guidelines about when to refer children, when to treat them or when to follow up for reassessment. Examples of such practices are provided in Boxes 4–7. Of course, training and implementation tools also need to be consistent with the national programme's guidelines.

#### **4. Foster local expertise and leadership**

Additional expertise is needed in settings where TB is endemic, and greater attention is being given to childhood TB as part of reviews conducted by national TB control programmes. Child health workers at all levels of the health care system, including those working in the private sector, should be involved in diagnosing and treating children with TB. National champions of childhood TB and national paediatric associations should lead efforts to diagnose and treat children with TB, and work with national programmes to educate paediatricians and other health workers about childhood TB. Efforts to educate health care workers should include providing information on the public health aspects of childhood TB and guidance on how they can become involved in developing, implementing and monitoring activities that focus on childhood TB.

Box 5 lists steps that could be taken to improve engagement with activities to address childhood TB, as identified and agreed by representatives of national TB-control programmes from eastern and southern Africa.

#### **Box 5. Steps to improve the diagnosis and care of children with TB identified by national TB control programmes from eastern and southern Africa at a meeting to discuss best practices in tuberculosis control, Kigali, Rwanda, 2010**

- Adapt international strategies and develop national guidelines for diagnosing and treating children with TB.
- Operationalize the guidelines addressing childhood TB.
- Identify someone to champion the cause of children with TB.
- Establish a working group on childhood TB at each national TB programme, and identify a person at the programme who will develop links with paediatricians and national paediatric associations.
- Provide training about childhood TB, and incorporate it into continuing education on TB and TB/HIV coinfection.
- Incorporate activities to address childhood TB into annual plans and five-year strategic plans.
- Ensure that national TB programmes incorporate activities addressing childhood TB into their budgets.
- Include data on TB in children in routine reporting and in reviews of national TB programmes.
- Develop and implement operational research to determine the constraints and barriers to diagnosing and treating children.
- Implement research aimed at improving the diagnosis and treatment of children with TB and the care of children who are contacts of someone with TB.

### Box 6. What can be achieved: experiences in Kazakhstan

An extensive review of the national TB control programme in the Republic of Kazakhstan was conducted by a WHO mission in May 2012, which found that the government is strongly committed to preventing TB in children and to caring for those with TB. Kazakhstan has an extensively developed infrastructure of paediatric TB services that focus on active case-finding among children and screening children who are contacts of someone with TB. TB notification rates among children decreased by about 74% from 1999 to 2011, from 57.6/100 000 population to 15.1/100 000 population. A decrease in TB notification rates was also observed among adolescents, from 161/100 000 in 2002 to 97.6/100 000 in 2011; however, as is the case in most of the WHO European Region, the reported rates of MDR-TB have increased threefold among children, and almost fivefold among adolescents.

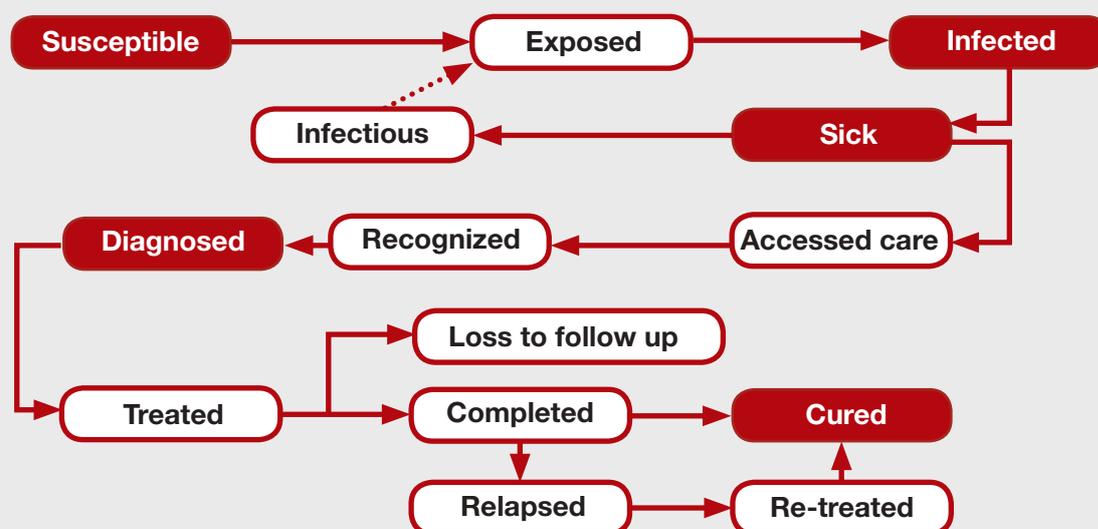
The review of the national TB control programme highlighted several important achievements the programme has made in addressing childhood TB:

- The majority of cases are diagnosed through active case-finding in the primary health care setting.
- Contact investigations in households with TB cases are conducted routinely.
- A well-developed network of paediatric TB services exists; this includes paediatricians available at the central and district levels, and hospitals and sanatoria that specialize in treating children with TB.
- Routine access to bacteriological diagnosis for TB in children (that is, culture and drug-susceptibility testing) is available.
- Paediatric formulations of anti-TB medicines are available, and children have access to first-line and second-line treatments.
- Standards are excellent for recording and reporting TB in children and adolescents.

### 5. Do not miss critical opportunities for intervention

One challenge to TB control is that TB comprises a continuum of health states, ranging from susceptibility to cure (Figure 2).<sup>11</sup>

Figure 2. Transitions in tuberculosis: from susceptibility to cure



Modified and reproduced with permission of the European Respiratory Society *European Respiratory Society Monograph 2000; 15 (Respiratory Epidemiology in Europe): 67–91.*

11 Enarson DA, Ait-Khaled N. Tuberculosis. In: Annesi-Maesano I, Gulsvik A, Viegi G, eds. *Respiratory Epidemiology in Europe. European Respiratory Monographs 2000; 15: 67–91.*

**Table 1. Transitions in TB and opportunities for intervention**

<b>Stage</b>	<b>Opportunity for intervention</b>
Susceptible, exposed	<p><b>PREVENT INFECTION</b></p> <p>Improve TB control in the community</p> <p>Improve infection control</p>
Infected	<p><b>PREVENT DISEASE</b></p> <p>Implement screening for children who are contacts of someone with TB</p> <p>Manage the care of children who are contacts of someone with TB</p> <p>Provide preventive therapy to all children younger than five years and all HIV-positive children</p> <p>Record and report delivery of isoniazid preventive therapy (IPT)</p>
Sick, accessed care, recognized	<p><b>DIAGNOSE DISEASE</b></p> <p>Suspect TB in children who are contacts of someone with TB or who have typical signs and symptoms</p> <p>Recognize typical signs and symptoms of TB at all levels of the health care system</p> <p>Ensure that capabilities exist to diagnose TB at least to a secondary level of care</p> <p>Recognize danger signs, such as respiratory distress or severe malnutrition, and refer to the appropriate level of care</p> <p>Ensure that referral systems are in place for children identified by health care providers as well as to refer complicated cases or very sick children to a higher level of care</p>
Treatment completed, cured, outcome	<p><b>SUPPORT CHILDREN AND THEIR FAMILIES</b></p> <p>Ensure that treatment follows national guidelines</p> <p>Ensure that appropriate medicines are available, including those for drug-resistant TB</p> <p>Provide care for HIV infection</p> <p>Develop or implement strategies to improve treatment completion rates and prevent loss to follow-up</p> <p>Record outcomes</p>
Register, record, report	<p><b>REPORT ACCURATE DATA, MONITOR AND EVALUATE SERVICES, ENGAGE IN ADVOCACY AND OPERATIONAL RESEARCH</b></p> <p>Ensure that all health care workers know that they are responsible for registering all children with TB</p>

Of course, not all susceptible children will advance through all or even most of the steps from susceptibility to cure, but the figure provides a useful framework for considering an individual's risks and the interventions that may potentially reduce those risks. At each stage lies the possibility of intervening and reducing morbidity and mortality (Table 1). Stakeholders involved in TB play different roles along the continuum, and have different opportunities to intervene. Opportunities to provide effective interventions must not be missed. Prevention is the ultimate goal; hence, every opportunity must be taken to implement intensified case-finding, contact-tracing and preventive therapy.

The effectiveness of interventions depends on the availability of the tools necessary for implementation, especially those for diagnosis and treatment. Good quality chest radiography is commonly required for diagnostic assessment. Methods for obtaining specimens, and laboratory techniques that provide a higher yield than microscopy, are improving. The global scale-up of the Xpert MTB/RIF diagnostic test offers an important opportunity for children to have access to rapid bacteriological diagnosis. It is essential that an uninterrupted supply of quality assured anti-TB medicines for children, including for preventive therapy, is available. There is a need for fixed-dose combinations of first-line anti-TB medicines that conform to the recommendations made in the 2010 revision of *Rapid advice: treatment of tuberculosis in children*;<sup>12</sup> there is also a need for paediatric formulations that can be readily used for young children.

## 6. Engage key stakeholders

Effective communication and collaboration among the health care sector and other stakeholders is increasingly seen as a key component to ensuring the success of health interventions. Table 2 describes the key stakeholders in childhood TB that should engage with one another, and highlights the main roles that each has the potential to fulfil.

### Box 7. Increased case-finding and preventive therapy: experiences in Pakistan

Following the initiation of a programme to deliver isoniazid preventive therapy as part of the Indus Hospital paediatric TB programme, it was noted that the enrolment rate of children was low, despite an average of 350 adults being enrolled in the TB preventive programme for adults each month (of which 54% were females of reproductive age). Some of the measures used to increase paediatric enrolment as well as paediatric TB case-detection included:

1. actively involving physicians, treatment supporters and counsellors from the TB programme for adults to encourage them to remind parents with sputum smear-positive pulmonary TB of the need for children aged younger than five years to be seen at the paediatric clinic for an evaluation;
2. screening all children younger than five years attending the Expanded Programme on Immunization for a routine visit; screening includes taking a basic contact history and a symptom screening for possible TB disease; children are referred to the paediatric TB programme if either screening is positive;
3. conducting basic contact screening and symptom screening for all malnourished children enrolled in the nutrition clinic; children are referred to the paediatric TB programme if either screening is positive;
4. implementing an awareness campaign that included posters, billboards and the involvement of general practitioners.

Notifications of cases of paediatric pulmonary TB at the hospital increased by a factor of seven using these approaches to childhood TB case-finding.

<sup>12</sup> *Rapid advice: treatment of tuberculosis in children*. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13). (Available from [http://whqlibdoc.who.int/publications/2010/9789241500449\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241500449_eng.pdf)).

**Table 2. Key stakeholders and their roles in addressing childhood TB**

Stakeholder	Main roles
<b>POLICY-MAKERS</b>	
<b>Global policy-makers</b>	<ul style="list-style-type: none"> <li>• Collaboratively address childhood TB across disciplines by providing leadership and guidance</li> <li>• Develop policies, strategies and guidelines for the management of childhood TB that are based on the best evidence</li> <li>• Provide support so that activities aimed at addressing childhood TB can be adopted at the national level; support may include training, tools, data-collection systems, technical support and the monitoring and evaluation of activities</li> <li>• Help define research needs for childhood TB and TB/HIV coinfection</li> </ul>
<b>National policy-makers (including national TB-control programmes as well as other relevant stakeholders)</b>	<ul style="list-style-type: none"> <li>• Provide high-level support throughout a country to assist in the scaling up of childhood TB services</li> <li>• Develop a framework to address TB in women and children that includes collaboration among national disease control programmes (for example, among those addressing TB, HIV, and maternal and child health) and national leaders in children’s health care (see Box 5)</li> <li>• Include childhood TB in the strategic plans and budgets of national TB programmes</li> <li>• Ensure that guidelines on caring for children with TB or HIV, or both, are adopted and implemented; ensure that data on childhood TB are collected, reported and recorded, and that staff have appropriate training</li> <li>• Support or perform operational research to improve activities aimed at addressing childhood TB (see additional information for Researchers below)</li> </ul>
<b>RELEVANT NATIONAL HEALTH-CARE PROGRAMMES</b>	
<b>Maternal and child health services</b>	<ul style="list-style-type: none"> <li>• Ensure that children and pregnant women are screened, diagnosed and treated for TB; this is especially important for HIV-positive women</li> <li>• Give TB preventive therapy when indicated</li> <li>• Provide appropriate care for neonates exposed to TB</li> <li>• Engage community health services in TB control activities, such as contact tracing</li> <li>• Record and report TB cases to the national TB programme</li> </ul>
<b>HIV services</b>	<ul style="list-style-type: none"> <li>• Ensure antenatal screening is implemented for HIV and TB</li> <li>• Ensure all children exposed to or infected with HIV are regularly screened for TB</li> <li>• Provide preventive therapy to HIV-positive children according to national guidelines</li> <li>• Ensure that all children exposed to or infected with HIV are screened for TB, and diagnosed and treated promptly</li> </ul>
<b>Health education institutions</b>	<ul style="list-style-type: none"> <li>• Ensure that childhood TB is adequately discussed in the standard curricula for all levels of health workers</li> <li>• Incorporate information on childhood TB into continuing training, in keeping with national guidelines</li> </ul>

Stakeholder	Main roles
<b>SPECIFIC HEALTH ACTORS</b>	
<b>Private health-care sector</b>	<ul style="list-style-type: none"> <li>• Ensure that children with TB are managed according to national guidelines</li> <li>• Report all children with a diagnosis of TB to the national TB programme</li> </ul>
<b>Community-based organizations and nongovernmental organizations</b>	<ul style="list-style-type: none"> <li>• Support local programmes according to capacity. This may include supporting initiatives aimed at increasing community education and awareness, or providing contact tracing, preventive therapy, TB diagnosis, and treatment or referral</li> <li>• Provide technical assistance and training if appropriate</li> </ul>
<b>Community leaders</b>	<ul style="list-style-type: none"> <li>• Promote TB education and awareness</li> <li>• Help the community to understand TB and its treatment to decrease the stigma associated with the disease</li> <li>• Support case-finding efforts and adherence to treatment</li> <li>• Promote the empowerment of children and families affected by TB by engaging them to help the community better understand the disease</li> </ul>
<b>Researchers</b>	<ul style="list-style-type: none"> <li>• Develop child-friendly, point-of-care diagnostics</li> <li>• Develop child-friendly formulations of anti-TB medicines</li> <li>• Develop improved or novel vaccines, or both</li> <li>• Continue work to fill the many knowledge gaps that exist (see point 7 below)</li> </ul>
<b>Advocacy groups</b>	<ul style="list-style-type: none"> <li>• Promote education and awareness</li> <li>• Help the community understand TB and its treatment to decrease the stigma associated with the disease</li> <li>• Advocate for resource mobilization</li> <li>• Provide input into national and international policy-making.</li> </ul>

## 7. Develop integrated family-centred and community-centred strategies

Attention is increasingly being focused on the importance of integrating the diagnosis, treatment and prevention of childhood TB into maternal, neonatal and children's health services when feasible or appropriate. In addition, it is important that coordination and communication are improved among different service providers to ensure that comprehensive services are delivered more effectively in the community. Shifting to a family-centred or community-centred approach requires effective collaboration and joint planning among TB control programmes, maternal and children's health services, and HIV services. Improving TB services for mothers will be crucial to efforts to improve services for children. As much as possible, TB services for children should be mainstreamed into existing children's health services, and more responsibility and accountability should be given to primary care providers.

While the exact mechanisms for incorporating childhood TB services into other health programmes will vary, several widely used programmes present clear opportunities for coordination and integration (Box 8).

### Box 8. Programmes into which TB services can be integrated

- Integrated management of pregnancy and childbirth (IMPAC) →
- Integrated management of childhood illness (IMCI) →
- Integrated community case management (iCCM) →
- Child HIV care programmes →
- Prevention of mother-to-child transmission of HIV (PMTCT) →
- Nutritional programmes for children →
- Family planning and fertility services →

Implementing TB services into these programmes will be challenging since there is little operational research that defines the optimal scope of services that should and can be provided. For each programme, tools will be needed to prompt health care workers to ascertain the necessary information, ask follow-up questions and take the appropriate actions. Nongovernmental organizations, community-based organizations and other civil-society organizations may be instrumental in improving services for childhood TB. There are several critical areas of TB control that are a natural fit for community-level efforts, such as increasing case-finding, offering treatment support, providing advocacy for and supporting patients and their families, providing training for and supervision of community health workers and volunteers, and implementing research.

### 8. Address research gaps

Research has a key role to play in the development, implementation and refinement of new tools, policies and programmatic interventions that aim to effectively prevent and manage childhood TB. There are fundamental differences between children and adults in terms of the underlying immunology, diagnosis, treatment and management of TB that need special attention from the global research agenda. The *International roadmap for TB research* was developed by the Stop TB Partnership's Research Movement, and formally launched at the October 2011 conference of the International Union Against Tuberculosis and Lung Disease in Lille, France.<sup>13</sup> The international roadmap prioritizes research in six main areas with the aim of eliminating TB by 2050: epidemiology, fundamental research, diagnostics, treatments, vaccines, and operational research. These priorities are described below with a special focus on children.

#### i. Epidemiology

- Better define the burden of disease in women, adolescents and children; this includes conducting nationwide inventory surveys to measure the underreporting and, if possible, under-diagnosis of childhood TB.
- Improve recording and reporting systems to capture all TB cases, and report data disaggregated by age and sex.
- Improve the understanding of variations in the dynamics of TB in different settings, and the social, environmental and biological drivers of the transmission of *M. tuberculosis* in different settings.
- Conduct evaluations to understand better the epidemiology of TB and TB/HIV coinfection in adolescents.

<sup>13</sup> *An international roadmap for tuberculosis research: towards a world free of tuberculosis*. Geneva, World Health Organization, 2011. (Available from <http://www.stoptb.org/assets/documents/resources/publications/technical/tbresearchroadmap.pdf>).

## **ii. Fundamental research**

- Characterize human TB using modern biochemical, clinical and epidemiological approaches, and address issues specific to improving the understanding of TB in children.
- Better understand the host–pathogen interaction; this includes improving understanding of the immune system in children in relation to its responses to mycobacterial infection at different ages.
- Apply discovery science to identify biomarkers that better differentiate the various stages of the disease spectrum and distinguish between infection and disease in children.

## **iii. Development of new diagnostics**

- Evaluate new diagnostics, and determine whether they are useful for confirming the diagnosis of TB in children.
- Develop diagnostics suitable for use with paediatric samples.
- Develop point-of-care diagnostics for use in children.

## **iv. Development of new anti-TB medicines**

- Identify the optimal doses for children of new and existing anti-TB medicines and regimens.
- Identify the optimal treatment duration and dosing of rifampicin-based treatment for children.
- Identify aspects of the design of clinical trials that can be tailored specifically for studies in children in regards to end-points, sample size, inclusion criteria, and at what point studies should assess the use of new anti-TB medicines in children.
- Determine whether new and existing medicines for which data on safety or toxicity in children are missing are suitable for use in children.

## **v. Development of new vaccines**

- Define suitable clinical end-points and immunological markers for vaccine trials in children.
- Improve clinical trials of vaccines in infants and children by conducting pre-vaccine epidemiological studies in order to standardize protocols, assays and methodological and clinical parameters.
- Develop improved vaccines for prime-boost vaccination that are safe and efficacious in preventing TB in children (including in those living with HIV), and define optimal conditions for their use in children, including defining the best ages for vaccination.

## **vi. Operational and public health research**

- Strengthen the recording and reporting of TB; improve global estimates of childhood TB (including drug-resistant TB in children); promote case-based electronic recording and reporting systems that can facilitate the compilation and analysis of data disaggregated by age.
- Advocate for and promote the development and establishment of vital registration systems that have national coverage.
- Determine the best approaches for identifying children who have been exposed to TB and determine how best to provide preventive therapy for children who are contacts of someone with TB and for children who are HIV-positive.
- Develop an evidence base for preventive therapy for children exposed to drug-resistant TB.

- Improve collaboration among TB services and other child-care services to increase TB case-finding.
- Within the general context of health care services and efforts to expand community-based care address issues specific to children in terms of case-finding, screening, access to diagnostics, access to treatment and the delivery of treatment, interactions between TB and HIV programmes, and infection control; answer the following questions:
  - How can collaboration between TB services and HIV services in maternal and child health settings be improved?
  - How can programmes to prevent mother-to-child transmission of HIV be used to ensure that both HIV-positive and HIV-negative women receive appropriate TB screening during pregnancy?
- Identify the unique needs and concerns of adolescents; pilot test, evaluate and scale up optimal approaches to addressing TB and TB/HIV co-infection among adolescents.
- Investigate how to optimize TB case-finding in children and adolescents; determine how to best measure the impact of intensive or enhanced case-finding on mortality and other outcomes.
- Determine the value of TB screening strategies in antenatal care programmes, HIV programmes, and maternal and child health programmes; determine ways in which screening can be operationalized.
- Develop and evaluate models of how to implement sustainable collaboration with all private and public providers of TB care and control services.

Evaluate how pregnant women and children are being or will be addressed during the roll-out and scaling up of the use of new diagnostic tests and new treatment or preventive regimens.

In addition to the areas outlined in the research roadmap and described above, there is a need to strengthen the evidence that supports the integration of care for childhood TB into other child care services, such as those models that address malnutrition, deliver integrated community case management (iCCM) and integrated management of childhood illness (IMCI). Evidence is also needed about the impact that these efforts have on case-finding and child survival. Models need to be developed to determine how to best integrate childhood TB interventions into other child-health services.

## 9. Meet funding needs for childhood TB

The Stop TB Partnership *Global plan to stop TB 2011–2015* estimates that during 2012–2015, US\$ 7.7 billion will be needed for research and development into TB (this represents the amount needed for all age groups).<sup>14</sup> Of this, at least US\$ 0.2 billion will be required to complete projects directly aimed at providing new tools for preventing, diagnosing and treating TB among children. At present, only 32% of the funding needed for research and development in TB is available.

In addition to the funding needed for research and development, funds are also required to implement interventions addressing childhood TB, including preventive measures. National TB programmes face significant challenges because of the lack of funding.

WHO has been monitoring funding for TB since 2002, and can assess the funding needs, availability and trends in countries that carry an estimated burden of 94% of the world's TB cases. However, funding requirements for child-specific TB interventions

<sup>14</sup> *Global plan to stop TB 2011–2015*. Geneva, World Health Organization, 2010 (WHO/HTM/STB/2010.2). (Available from [http://www.stoptb.org/assets/documents/global/plan/TB\\_GlobalPlanToStopTB2011-2015.pdf](http://www.stoptb.org/assets/documents/global/plan/TB_GlobalPlanToStopTB2011-2015.pdf).)

– such as diagnosis using sputum induction, treatment using paediatric fixed-dose combinations of medicines or the provision of child-specific training – have not been highlighted in recent national strategic plans, nor have they been specifically requested during the annual collection of TB data by WHO.<sup>15</sup>

In a first attempt to put a global price tag on implementing interventions aimed at childhood TB for the period 2011–2015, detailed funding requirements for seven countries were calculated (Bangladesh, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Pakistan and South Africa). Together these countries account for an estimated 64% of the burden of childhood TB worldwide. The method used to calculate the cost of implementing interventions for childhood TB used the ingredients approach embedded in the WHO tool for planning and budgeting for TB activities.<sup>16</sup> The funding requirements for the remaining 36% of TB cases occurring in children were extrapolated by adjusting each country's per capita gross domestic product. Preliminary results of the detailed cost estimations show that implementing the recommended TB interventions would mean investing between US\$ 84 and US\$ 319 for each case of childhood TB.

This analysis estimates that US\$ 80 million per year will be required to address childhood TB. An additional US\$ 40 million per year will be needed for antiretroviral therapy and co-trimoxazole preventive therapy for children coinfecting with TB and HIV (these treatments are usually funded by HIV programmes). These estimates probably underestimate the financial effort required because the burden of TB disease among children is probably greater than the notifications of cases younger than 15 years of age. Better assessments of the funding needed for the future depend on improving the monitoring and evaluation of the burden of disease in children, and systematically including interventions aimed at childhood TB in national strategic plans.

## **10. Form coalitions and partnerships to improve tools for diagnosis and treatment**

It is essential to work with industry, academia, major agencies, nongovernmental and other organizations involved in the development and evaluation of diagnostics and therapeutics. Much of the data on pharmacokinetics that is necessary to determine optimal treatments for infants and children is gathered only after a new medicine has been licensed – that is, after Phase III testing. However, it is more appropriate to gather basic pharmacokinetic data for infants and children after Phase II studies have been completed, when the medicine has been shown initially to be safe in adults. Gathering data after Phase II studies would also allow for child-appropriate and child-friendly formulations of the medicine to be developed as progress towards licensing ensues.

Because the burden of TB and MDR-TB varies by country, and the resources available to address it also vary, collaboration and partnerships are important. For example, even in countries with a high burden of TB, few areas recognize and treat enough cases of MDR-TB in children to be able to evaluate the best strategies for prevention and care. However, by pooling data and information from many sources, more robust clinical and research agendas can be addressed. Similarly, research that evaluates novel diagnostics, medicines or regimens often requires a large number of confirmed cases. Therefore, multisite collaborative work is necessary, and this may also contribute to building capacity across a wide range of settings where TB is endemic.

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<sup>15</sup> Updated data are available each year from: <http://www.who.int/tb/data>

<sup>16</sup> Available at: [http://www.who.int/tb/dots/planning\\_budgeting\\_tool/en/index.html](http://www.who.int/tb/dots/planning_budgeting_tool/en/index.html)

# ROADMAP FOR CHILDHOOD TUBERCULOSIS



Include the needs of children and adolescents in research, policy development and clinical practices



Collect and report better data, including data on prevention



Develop training and reference materials for health care workers



Foster local expertise and leadership



Do not miss critical opportunities for intervention



Engage key stakeholders



Develop integrated family-centred and community-centred strategies



Address research gaps



Meet funding needs for childhood TB



Form coalitions and partnerships to improve tools for diagnosis and treatment



WHO/Damien Schumann

## Achieving zero deaths

The recent and marked increase in attention being paid to TB in children provides an important opportunity to address the existing gap between policies and practice; addressing this gap may increase detection and improve the case management and prevention of TB in children. This roadmap is a response to this opportunity, and has identified top challenges and priorities for addressing childhood TB in order to facilitate progress by charting a way forward. Reaching zero TB deaths and eventually eliminating TB in children worldwide is possible but requires sustained advocacy, mobilization of adequate resources, and a joint effort by all stakeholders involved in children's health care and TB control.



C.Powell

# Resources

## Guidance and guidelines

- *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries*. Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.9) (Available from [http://apps.who.int/iris/bitstream/10665/77741/1/9789241504492\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/77741/1/9789241504492_eng.pdf)).
- *An international roadmap for tuberculosis research: towards a world free of tuberculosis*. Geneva, World Health Organization, 2011. (Available from <http://www.stoptb.org/assets/documents/resources/publications/technical/tbresearchroadmap.pdf>).
- *Guidance for national tuberculosis and HIV programmes on the management of tuberculosis in HIV-infected children: recommendations for a public health approach*. Paris, International Union Against Tuberculosis and Lung Disease, 2010. (Available from <http://www.theunion.org/index.php/en/resources/technical-publications/item/759-guidance-for-national-tuberculosis-and-hiv-programmes-on-the-management-of-tuberculosis-in-hiv-infected-children-recommendations-for-a-public-health-approach>).
- *Rapid advice: treatment of tuberculosis in children*. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13). (Available from [http://whqlibdoc.who.int/publications/2010/9789241500449\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241500449_eng.pdf)).
- *Global plan to stop TB 2011–2015*. Geneva, World Health Organization, 2010 (WHO/HTM/STB/2010.2). (Available from [http://www.stoptb.org/assets/documents/global/plan/TB\\_GlobalPlanToStopTB2011Ð2015.pdf](http://www.stoptb.org/assets/documents/global/plan/TB_GlobalPlanToStopTB2011Ð2015.pdf)).
- *Ethambutol efficacy and toxicity: literature review and recommendations for daily and intermittent dosage in children*. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.365). (Available from [http://whqlibdoc.who.int/hq/2006/WHO\\_HTM\\_TB\\_2006.365\\_eng.pdf](http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.365_eng.pdf)).
- *Guidance for national tuberculosis programmes on the management of tuberculosis in children*. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.371). (Available from [http://whqlibdoc.who.int/hq/2006/WHO\\_HTM\\_TB\\_2006.371\\_eng.pdf](http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.371_eng.pdf)).
- *Revised TB recording and reporting forms and registers – version 2006*. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.373). (Available from [http://www.who.int/tb/dots/r\\_and\\_r\\_forms/en/](http://www.who.int/tb/dots/r_and_r_forms/en/)).

## Field guides and handbooks

- *Standards and benchmarks for tuberculosis surveillance: checklist and user guide*. Geneva, World Health Organization, 2013 (in press).
- *Community-based tuberculosis prevention and care: why and how to get involved*. Washington, DC, CORE group, 2013. (Available from [http://www.coregroup.org/storage/TB/Community-Based\\_TB.pdf](http://www.coregroup.org/storage/TB/Community-Based_TB.pdf)).
- *Assessing tuberculosis under-reporting through inventory studies*. Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.12). (Available from [http://apps.who.int/iris/bitstream/10665/78073/1/9789241504942\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/78073/1/9789241504942_eng.pdf)).
- *Management of multidrug-resistant tuberculosis in children: a field guide*. Boston, Sentinel Project on Pediatric Drug-Resistant Tuberculosis, 2012. (Available from [http://sentinelproject.files.wordpress.com/2012/11/sentinel\\_project\\_field\\_guide\\_2012.pdf](http://sentinelproject.files.wordpress.com/2012/11/sentinel_project_field_guide_2012.pdf)).

- *Desk-guide for diagnosis and management of TB in children*. Paris, International Union Against Tuberculosis and Lung Disease, 2010. (Available from [http://www.ups.upenn.edu/bugdrug/antibiotic\\_manual/iautldtbkidsdxx2010.pdf](http://www.ups.upenn.edu/bugdrug/antibiotic_manual/iautldtbkidsdxx2010.pdf)).

### Advocacy documents

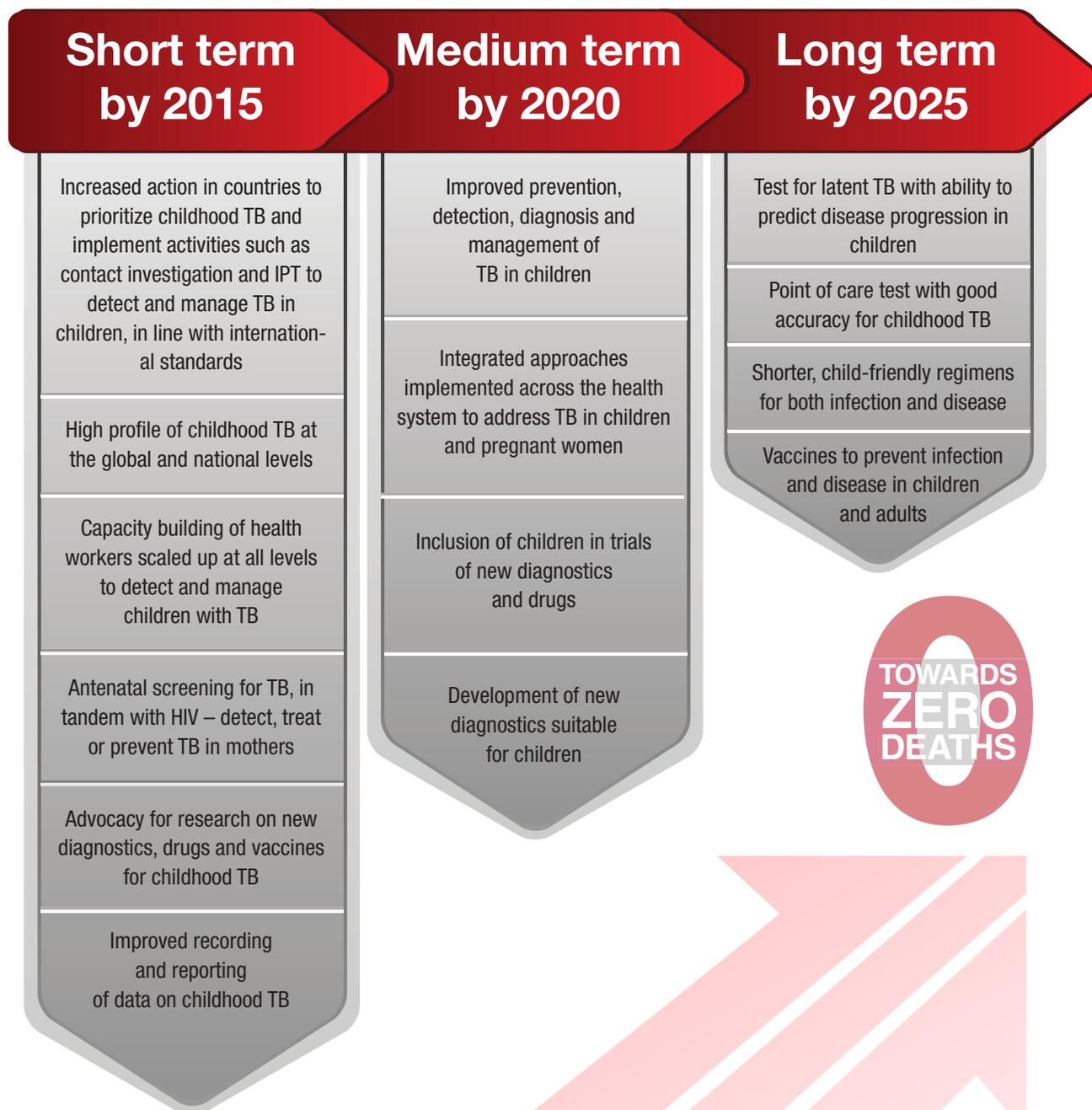
- *We can heal. Prevention, diagnosis, treatment, care, and support: addressing drug-resistant tuberculosis in children*. Boston, Treatment Action Group, Sentinel Project on Pediatric Drug-Resistant Tuberculosis, 2013. (Available from <http://www.treatmentactiongroup.org/tb/publications/2013/we-can-heal>).
- *Being brave: stories of children with drug-resistant tuberculosis*. Boston, Sentinel Project on Pediatric Drug-Resistant Tuberculosis, 2012. (Available from <http://www.treatmentactiongroup.org/sites/tagone.drupalgardens.com/files/SP%20report%20v3.pdf>).
- *Children and tuberculosis: from neglect to action*. Washington, DC, Action, 2012. (Available from [http://www.action.org/images/general/Children\\_and\\_TB\\_Update\\_-\\_English\\_%284%29.pdf](http://www.action.org/images/general/Children_and_TB_Update_-_English_%284%29.pdf)).
- *No more crying, no more dying: towards zero TB deaths in children*. Geneva, World Health Organization, 2012. (Available from [http://www.stoptb.org/assets/documents/resources/publications/acsm/ChildhoodTB\\_report\\_singles.pdf](http://www.stoptb.org/assets/documents/resources/publications/acsm/ChildhoodTB_report_singles.pdf)).
- *Children and tuberculosis: exposing a hidden epidemic*. Washington, DC, Advocacy to Control TB Internationally, 2011. (Available from [http://gallery.mailchimp.com/df2764cb26f191f347018e3b6/files/Children\\_and\\_TB\\_Report.pdf](http://gallery.mailchimp.com/df2764cb26f191f347018e3b6/files/Children_and_TB_Report.pdf)).
- *Out of the dark: meeting the needs of children with TB*. Geneva, Médecins Sans Frontières, 2011. (Available from <http://www.msfaccess.org/content/out-dark-meeting-needs-of-children-with-TB>).

### Web sites

- Childhood tuberculosis: <http://www.childhoodtb.org>
- CORE Group: Pediatric tuberculosis (Pediatric TB Interest Group): <http://coregroup.org/our-technical-work/working-groups/tuberculosis>
- International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT): <https://impaaactgroup.org/>
- Paediatric TB Network in Europe (pTbNet): <http://www.tb-net.org/index.php/about-us/ptbnet>
- Sentinel Project on Pediatric Drug-Resistant Tuberculosis: <http://sentinel-project.org/>
- Stop TB Partnership: Childhood TB Subgroup of the DOTS Expansion Working Group: [http://www.stoptb.org/wg/dots\\_expansion/childhoodtb/](http://www.stoptb.org/wg/dots_expansion/childhoodtb/)
- Stop TB Partnership: New Diagnostics Working Group of the Childhood TB Subgroup: <http://www0.sun.ac.za/NDWGChildTB/>
- The International Union Against Tuberculosis and Lung Disease: Childhood tuberculosis: <http://www.theunion.org/index.php/en/what-we-do/child-lung-health-/childhood-tb>
- The International Union Against Tuberculosis and Lung Disease: Child lung health: <http://www.theunion.org/index.php/en/what-we-do/child-lung-health->
- Treatment Action Group: Childhood TB: <http://www.treatmentactiongroup.org/tb/advocacy/forgotten-not-gone-childhood-tb>
- United States Centers for Disease Control and Prevention: Tuberculosis: <http://www.cdc.gov/tb/topic/populations/TBinChildren/default.htm>
- WHO: Childhood tuberculosis: <http://www.who.int/tb/challenges/children/en/index.html>



# TIMELINE: KEY ACTIONS TO ADDRESS CHILDHOOD TB



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