

Childhood Tuberculosis Roadmap
full text DRAFT, 22 Oct 2012

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PREFACE

It has been estimated that in 2011 there were 8.7 million (range, 8.3-9.0 million) people who fell ill from tuberculosis (TB) and that at least half a million were children (< 15 years old). Of these, an estimated 1.4 million (range, 1.3-1.6 million) people died from TB, among whom as many as 70,000 were HIV-uninfected children. Further, in 2009 there were an estimated 9.7 million children (range, 8.5-11 million) living in the world that had been orphaned as a result of parental deaths caused by TB.

These numbers do not tell the whole story. The true burden of TB-related morbidity and mortality among children is not known for a number of reasons which would result in an underestimation: difficulties with access to diagnosis and care in this vulnerable population; clinical overlap with other common diseases of childhood can result in many cases being missed; many children treated for TB outside of national TB programmes (NTPs) are not registered; and a lack of routine practice of recording and reporting of all child TB cases by age and outcome by some National TB Programmes (NTPs). On the other hand, diagnostic uncertainty is very common in children treated for TB and this can result in over-diagnosis especially for pulmonary TB.

The need for increased attention to the challenges of TB in children as an integral part of national TB control activities has been highlighted by child TB advocates for decades. In recent years, as the Stop TB Strategy for TB control has expanded beyond DOTS to intensify case-finding among vulnerable populations (in 2006) and formulates strategies for the future (beyond 2015) to include attention to community-based care, integration and preventive care, the need for increased attention to TB in children is beginning to receive some genuine attention at global and national levels.

Another compelling reason for the need to address TB in children is that TB is an important cause of child morbidity and mortality, whether directly or indirectly affected by maternal morbidity and mortality. The recent high-level Child Survival: Call to Action meeting facilitated by USAID and UNICEF promoted the ambition that “every child should have a fifth birthday”. This will not be achievable without attention to children with TB and to children who are close contacts of persons with infectious TB or HIV.

We know that TB is an important cause of death in children from autopsy studies, from the reported high mortality of infants and young children with disseminated disease, and from observational studies reporting high all-cause mortality in children living in households with persons with infectious TB. What we do not know is the contribution of TB as a cause of the childhood deaths that are attributed in global statistics to pneumonia, malnutrition and meningitis, but it may be substantial. It is likely to become relatively even more important as there is a continuing fall in deaths due to the recognised “major killers” in children such as pneumonia, malnutrition, diarrhoea and malaria.

Children with TB present to health services in the same context as all the other common childhood illnesses. Newborns and infants of mothers with TB attend maternal care services and have special management challenges that require coordination and communication across maternal and child health services. Children living with HIV may present with TB-related illness or contact in the context of the HIV clinic. Clearly, the usual setting for diagnosis and care is not the tertiary hospital but rather the primary and secondary care settings including those that provide care for adults with infectious TB, peri-natal care, HIV care, or nutritional rehabilitation support as well as outpatient and inpatient facilities that care for sick children. In fact, the most obvious entry point for many child TB cases or child TB contacts is at the community level of care where the parent/guardian/household contacts are being diagnosed and managed for TB.

The potential benefits and cost-benefits for increased access to care, quality of care and community-based preventive strategies by improved integration of services, improved communication between services and health workers, and improved community-based implementation and monitoring should be clear. This is entirely consistent with the expanded Stop TB Strategy as it strives to move not just beyond TB control to integrate with other health services, but even beyond the health care delivery services to include other services that are relevant to addressing the social determinants of health and equitable access to health care. But how can these goals be achieved?

NTPs are now increasingly striving to address the challenges of caring for children with TB and children that are TB contacts. There has been a lack of political will but this is beginning to change. National priorities are being identified and there is increasing input of NTP managers into international child TB activities. National policies and guidelines are being revised and redrafted. An increasing number of NTPs are forming working groups and dedicating staff to coordinate child TB activities. There have been recent training initiatives on child TB for NTPs including the development of tools for training at the primary and secondary level, and tools for evaluation. Training is critical and it is important that it becomes an integrated part of other relevant updates and training at all levels and settings of care for maternal and child health as well as ongoing NTP updates and training. It should be integrated into the curricula of health care worker undergraduate training such as in nursing and medical schools.

But pragmatic goals, clear guidelines, training and consistent messages may still not be enough to narrow the wide policy-practice gap that exists for implementation of effective strategies to protect children from TB. This has been well recognised in trying to provide an integrated approach to TB/HIV and has met with variable success for individuals and perhaps less so for families living with TB/HIV. Indeed, the three “I”s for TB control in persons living with HIV are all relevant to children especially child contacts whether HIV-infected or not.

Attention is now beginning to turn to this challenge of improving integration, coordination and communication to provide a more comprehensive and effective service at the community level. A major

challenge is that it is extremely difficult to provide generic “guidelines” or policy for integration as the settings, the existing health systems and their capabilities vary widely even within countries. The Stop TB Strategy recognises the needs to reach out beyond the public health sector to include the private health sector, non-governmental organisations, civil society, community groups and faith-based organisations. But this will require innovative approaches that break new ground in approaches to health care delivery, not just TB. Further, the acceptance that children can be part of a decentralised approach to TB control (especially contact symptom-based screening and management) is very recent and there are few examples of this in practice. In many settings, there even still needs to be political will. Policy makers might be better convinced by effective (and cost-effective) examples. Decentralising TB care for children is likely to be highly cost-effective by improving access, case-finding, early treatment and by not requiring a major increase in resources such as facilities or staff. This is a major opportunity for innovative approaches and operational research that could lead to improved TB control and improved child health care, that could inform better practice in a range of settings, and that could bring important benefits to vulnerable communities. As we finally get consensus on the “why”, we are faced with the more important question of “how”.

This roadmap seeks to tackle these difficult questions and chart a course to accelerate progress towards the elimination of childhood TB.

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WHAT?

The Silent Epidemic of Childhood TB

Globally, the World Health Organization (WHO) estimates that at least 500,000 children become ill with TB and as many as 70,000 HIV-negative children die from TB every year but recognizes that the current paucity of national level data available to inform these estimates means that they likely do not fully capture the global burden of childhood TB. In high TB burden settings, it is observed that 15-20% of all TB cases are among children as compared to low TB burden settings where an estimated 2-7% of all TB cases are among children.

Natural History of TB in Children

Exposure to infection

Any child that lives in a setting where there are persons with infectious TB can be exposed to *Mycobacterium tuberculosis*. The risk is highest for those that live in high TB and HIV-endemic communities, but can also be high in certain settings or among certain populations in low TB-endemic countries, such as congregate settings or among recent immigrants from a high TB-endemic setting. Children are usually infected with *M. tuberculosis* by inhalation into the respiratory system following exposure to a person with active TB who is coughing. The likelihood of infection following exposure is greatest when there is close (e.g. household) contact with a person with TB, and if that person has sputum smear-positive disease.

Infection

When primary infection of the lung occurs, bacilli multiply and drain to regional lymph nodes where cell-mediated immunity is activated to effect containment. The currently accepted biomarker of this immune response to infection is the tuberculin skin test (TST), which will usually become positive within 8-12 weeks of infection. Most children (around 90%) infected with *M. tuberculosis* will contain the infection and not develop symptoms, unless they are very young, HIV-positive or otherwise immune-compromised.

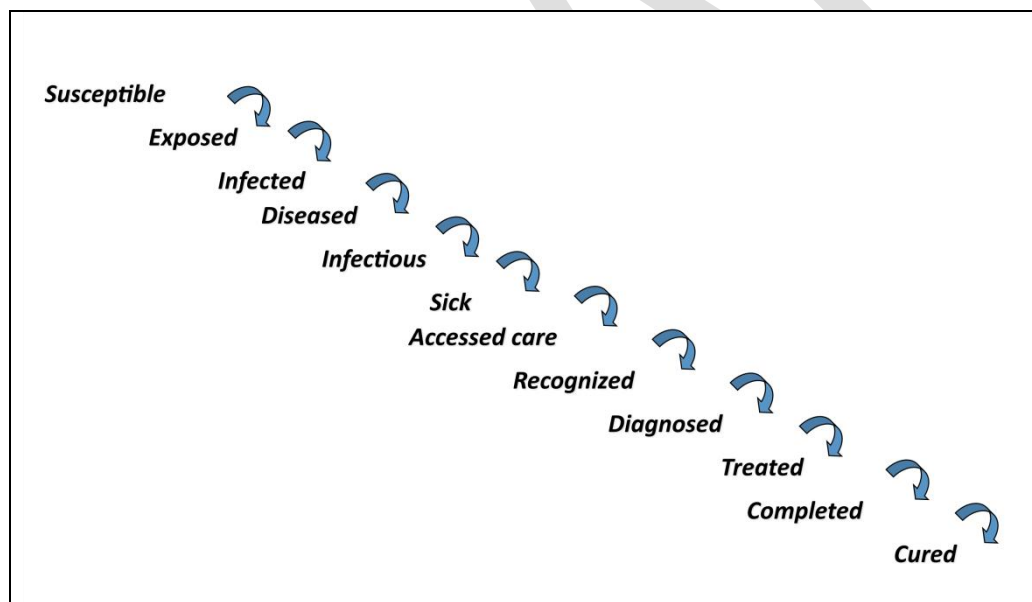
Infection to disease

Any child infected with *M. tuberculosis* may develop active TB disease. The majority of disease in children occurs within one year of primary infection, which is why a contact history is so relevant and why the burden of TB in children reflects on-going transmission in a population. Risk factors for developing disease following infection include young age (< 3 years) and immunodeficiency such as due to HIV, measles or severe malnutrition. Adolescence is another age group where there is an increased risk of developing disease.

Disease

Progression from infection to TB disease is indicated by the onset of typical symptoms. The most common type of TB disease in children is pulmonary TB. Extrapulmonary TB is also common (around 20-30% of all child TB cases), especially TB adenitis and TB pleural effusion. 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 presenting as TB meningitis or miliary TB, and of progressing more rapidly following infection to acute disease, with pulmonary TB presenting as acute, severe pneumonia. The most common type of pulmonary TB in children is classified as sputum “smear-negative” disease – which is strictly defined as sputum microscopy negative and is common because of the paucibacillary nature of TB disease in children, but often may in reality be sputum microscopy “not done” (but reported as “smear-negative”) because of difficulties in obtaining sputum from young children. Forms of TB in children where a strong immune response affects pathogenesis and therefore clinical presentation, such as TB adenitis, osteo-articular TB or TB with effusion (e.g. pleural, pericardial, peritoneal), are more common in older children (> 3 years). Adolescents are at particular risk of developing adult-type disease i.e. often sputum smear-positive and highly infectious.

Figure 1: Transitions in Tuberculosis



Ref: Enarson DA, Ait-Khaled N. Tuberculosis. In: *Respiratory Epidemiology in Europe*, Annesi-Maesano I, Gulsvik A, Viegi G, eds. Huddersfield: The Charlesworth Group, 2000: 67-91

Figure 1 sets out the steps that may occur in transition from being susceptible by living in an environment where *M.tuberculosis* is being transmitted through to the development of disease (i.e. TB) to cure. Of course, all susceptible children will not advance through all or even most of these steps but it provides a

useful framework for considering individual risks for progression to disease and potential interventions to reduce those risks; and then if progression is to disease, important steps on the pathway to consider to ensure the best possible outcome.

WHY?

Reasons for Historical Neglect of Childhood TB

Childhood TB has historically been neglected by NTPs and the health community in general for a number of reasons. First, the difficulty in confirming a case of childhood TB with the available microbiologic techniques and the limited availability and/or lack of tools to aid in the clinical diagnosis of TB (eg. chest radiography, tuberculin skin test) in many high burden settings has led to a certain fatalism about the ability to identify children with TB. Second, as children with TB are usually less infectious than adults, they have been assigned a low public health priority by NTPs that focus on the case detection and treatment of pulmonary sputum positive TB, hence on interruption of transmission of the organism. Third is the common misperception that childhood TB would disappear simply by the containment of TB in the wider population. However, modeling studies have shown that improvement in the detection and management of children with TB would have a far greater impact on the health of children than improved case detection and treatment of adults with pulmonary TB. Fourth, there has been a misplaced faith in the BCG vaccines. Although the BCG vaccines have been shown to prevent about 60 % to 90% of cases of meningeal and disseminated TB in young children, they do not prevent a high enough proportion of cases in children or adults to be an adequately effective measure of TB control. Fifth, the scientific study of childhood TB has been stymied by a lack of funding and interest from industry. This inattention derives partly from the difficulty with microbiologic confirmation of disease, but also originates in the reticence to conduct studies in children and from the perception that the market for any innovations in the diagnosis or management of childhood TB would be too small to justify the investment. Finally, there has been a lack of advocacy on behalf of children with TB from both the TB community and persons and organizations dedicated to child health and survival. The widely acknowledged under-reporting of childhood TB means that its impact on child survival has been underestimated and under-recognised by child health community at large, and practitioners and advocates in particular. There is a lack of recognition of its importance within existing child health programs, including programs serving some of the highest risk children such as programs for malnutrition and HIV/AIDS where TB screening, treatment and prevention have the potential to substantially reduce morbidity and mortality.

Barriers to Implementation and Scale-up of Childhood TB Activities

Childhood TB has historically not been a priority for NTPs for the reasons outlined above. Attention to child TB activities is rarely included in planning strategies and budgets for NTPs and NTP staff may have limited knowledge of/experience with child TB management issues, especially rationale for management approaches that might be specific to children. Furthermore, there is often a lack of data on the burden of

TB in children and how to address the challenges of child TB to inform NTP activities and their planning strategies (with budgets). National and international reporting of child TB cases is often incomplete because aggregation of data from TB registers does not retain sufficient data by WHO recommended paediatric age categories (0-4 years old and 5-14 years old) to generate national level data on children registered for TB treatment and because not all children treated for TB are captured in TB registers as children with TB may be cared for by practitioners/in health facilities in the private and public sector that do not report to the NTP. Treatment outcome in children treated for TB is not reported.

The recognised limitations of tools available for diagnosis of TB especially in young children create a perception (or misperception) that all children with suspected TB need to be referred to a higher level of care. There is often a perception (or misperception) that the treatment of young children with TB is more complicated or has an increased risk of toxicity than for older children or adults. These perceived needs for referral and for a tertiary level of care for all children with suspected TB are a major barrier to access for care. The perceived need for investigations - usually either unavailable or difficult and costly to access such as TST and CXR - in child contacts that do not have TB disease but require preventive therapy is a major barrier to implementation of child contact screening and management. Children with TB often live in poor and vulnerable families and communities where there is often poor access to health care. Finally, children generally do not access care directly; rather, they are reliant on a parent or guardian for access to evaluation and care.

HOW?

What Has Already Been Achieved

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 TB 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 U.S. Public Health Service, demonstrated the effectiveness of isoniazid in preventing the progression of infection to disease in both adults and children. Between the 1950s and the 1980s, research into childhood TB was somewhat sporadic and sparse, apart from some studies that demonstrated effectiveness and safety of “short-course” regimens of first-line antituberculosis drugs in children.

The emergence of the HIV epidemic provided many new challenges. In the 1990s, descriptions of the interaction between TB and HIV infection in children were published, and demonstrated that TB was a common cause of morbidity and mortality in HIV-infected children living in TB-endemic settings. However, research from high burden settings of TB in HIV-infected and uninfected children that informs epidemiology, diagnosis and treatment has been restricted to a few settings, largely because of limited

resources and infrastructure to conduct studies that include a large number of children with confirmed disease.

National and International Leadership and Guidance

The decade of 1995-2005 saw an unprecedented scale up of the DOTS strategy in high TB burden countries. The creation of the Childhood TB subgroup (under the DOTS Expansion Working Group of the Stop TB Partnership) in 2003 gave children a “seat at the table”, providing significant input into many initiatives of WHO, triggering increased attention to childhood TB and contributing to efforts to address childhood TB at global and country levels. The subgroup has been instrumental in developing and publishing many sets of evidence-based guidelines including:

- Guidance for national TB programmes on the management of TB in children was published by WHO in 2006
- WHO recommendation in 2006 that children should always be included in the routine NTP recording and reporting system and that NTPs should record and report two age groups for children (0-4 years and 5-14 years) using the quarterly reporting form along with other routine data such as related to TB/HIV
- In 2006, the Stop TB Partnership also changed its strategy to increase active case finding; this was a particularly important development for children as active case-finding can discover recently infected children before they have had the remarkable increase in disease expression that is the hallmark of passive case-finding.
- A research agenda for childhood TB, listing needs for the development of new tools followed in 2007
- Revision by WHO of the recommended drug dosages of the four first line anti-TB medicines for children (Rapid Advice on treatment of tuberculosis in children, 2010)
- Joint WHO and the Union's guidance for TB and HIV programmes on the management of TB in HIV-infected children (2009) and the Union's Desk guide for diagnosis and management of TB in children (2010)
- Guidance for national TB programmes on the management of tuberculosis in children: second edition published by WHO in 2012 (or 2013)

The International Child TB Training Workshop (Stellenbosch University/IUATLD) held in Cape Town annually since 2007 has provided training for child TB experts from many countries representing national programmes, public health services, research, education and NGO sectors. This has helped to foster leadership at national level and implementation of child TB-related activities by individuals who have attended this course as outlined below:

- **Development of national guidelines.** In the past, national TB programme guidelines provided very limited guidance for the management of TB in children, often just a few lines. The one policy that was consistently recommended was contact screening and management – and this was and still is rarely implemented. NTPs in many regions are now including comprehensive management guidelines for child TB either as separate guidelines).
- **Situational analysis and identification of national priorities.** NTPs have initiated external, critical reviews of child TB activities to identify gaps and priorities for implementation and evaluation, either as part of an overall NTP review or as a separate technical assistance that focuses on child TB.
- **Development of national leadership.** Development and implementation of guidelines require organisation and leadership at national level such as by a “child TB working group” that includes representative(s) of the NTP working with national child TB experts and advocates.
- **Training activities – implementation and evaluation.** Training is critical for implementation of updated guidelines to address the policy-practice gap in priority areas. Training of trainer initiatives have been conducted in high burden setting in Africa and Asia over the last 3 years and IEC/training tools have been or are being developed.

Growing Advocacy

Several important and even historic activities have occurred within the past three years. In 2011, an international childhood TB meeting sponsored by the Childhood TB subgroup and the European Centre for Disease Prevention and Control was held in Stockholm. This resulted in a Call to Action for Childhood TB and publication of the meeting notes in the *European Respiratory Journal*. Later that year, international experts in childhood TB met in Washington, DC to develop standardized definitions to be used in research protocols (resulting in two papers published in the *Journal of Infectious Diseases*). In 2011, the unmet needs of women and children with regard to TB were the focus of the Stop TB Symposium, opening the 42nd Union World Conference on Lung Health in Lille, France. In 2012, for the first time, childhood TB was the theme for World TB Day resulting in presentations to elected officials, advocates and new publications all over the world.

Several new initiatives have been developed with a focus on research including the formation of a Tuberculosis Scientific Committee within the International Maternal Pediatric adolescent AIDS Clinical Trials Group (IMPAACT) and the Sentinel Project on Pediatric Drug-resistant TB which is a global partnership of researchers, caregivers, and advocates that was convened and is hosted by the Department of Global Health and Social Medicine at Harvard Medical School and the National Institute for Research in Tuberculosis (Chennai, India) which is and aims to develop and deploy evidence-based strategies to prevent child deaths from this treatable disease.

Increasing Recognition of Importance of Addressing TB among Women 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 for pregnant women and their babies. Maternal TB 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 maternal and infant mortality. Important progress has been made towards achieving the Millennium Development Goals (MDGs). However, success in meeting the health-related MDGs will only be realised through a comprehensive approach. MDG 4 (child health) and 5 (maternal health) will not be reached without additional effort on TB diagnosis and treatment in mothers and children. As a result, there have been increasing calls for family-based approaches to TB/HIV so that:

- TB programmes work to remove barriers to access, reduce delays and improve diagnosis and treatment of TB in women and children
- All pregnant women and their infants in TB endemic countries are tested for HIV and screened for TB and these activities are incorporated into maternal and child health (MCH) programmes
- TB and HIV diagnostic, care, treatment and prevention services are scaled up to reach vulnerable women, children and their families

Adding a 4th “I” to the WHO and UNAIDS’ long recommended 3 “I” (intensified case finding, infection control and isoniazid preventive therapy) policy for addressing co-infection of TB and HIV -- that is integration of TB and HIV services within antenatal, PMTCT, family planning and immunization and other child health services will allow better care for pregnant women and their babies and will increase a likelihood of early detection of TB and prompt initiation of treatment – represents an important step towards achieving these goals).

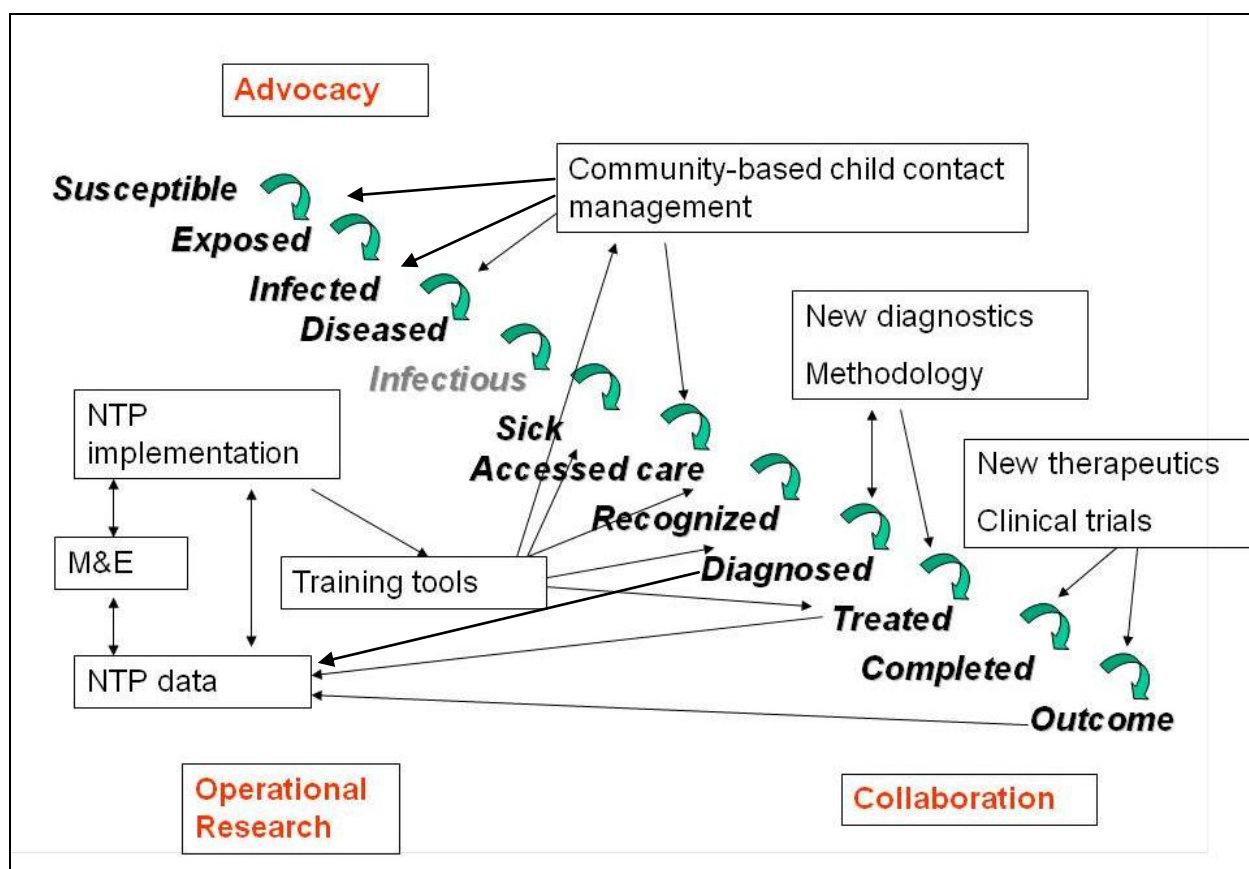
WHO? WHERE? WHEN?

Accelerating Progress Together – Critical Opportunities for Intervention

As noted earlier, TB is not a static disease entity, rather, it is more fully understood in a public health context as a continuum of states/transitions from susceptibility to cure. Each of these transitions has a measurable probability, which varies depending on factors such as the patient’s characteristics (e.g. immune status, age), and the organization and functioning of the health system (e.g. accessibility, availability of diagnostics and treatment). Delays at any of these steps will lead to increased morbidity, mortality and transmission of TB. Stakeholders involved in TB control have different roles and

responsibilities along the pathway, from increased awareness in the community, improved access to care to provision of quality services and treatment. Communication and collaboration is needed to ensure its optimal flow. Only when every step is addressed can TB, not only in children, be eliminated (Figure below).

Figure 2: Examples of Opportunities for Intervention at Points in Transitions in TB



1) Susceptible, exposed, infected = **PREVENT INFECTION**

- Older children can be infectious and contribute to transmission, which is often neglected.
 - Infection control measures can prevent transmission.
- Advocacy and awareness measures by health care providers, CBOs, NGOs are needed.*

2) Diseased, infectious, sick = **PREVENT DISEASE PROGRESSION**

- Being among the highly susceptible, children benefit most from preventive chemotherapy. Yet, it is only rarely implemented at the programme level. Recording and reporting of IPT is crucial.

TB programmes, CBOs, NGOs need to explore best approaches to identify and manage child TB contacts in the household and community. Other health care providers (CCH etc.) should be integrated.

3) Accessed care, Recognized, Diagnosed = **DIAGNOSE DISEASE**

- Once children arrive at any health care provider, TB needs to be suspected in the presence of typical signs and symptoms.
- Children can progress quickly from infection to disease to severe disease. Typical signs and symptoms of TB as well as danger signs need to be recognized and children referred to the appropriate level of care.
- Referral systems must be in place for children identified by other healthcare providers as well as for referral of complicated cases or very sick children to a higher level of care.
Collaboration between providers; training, supervision and mentoring are critical
- Point of care diagnostics suitable for child specimens needed to improve diagnosis of childhood TB

4) Treated, completed, cured = **ACCOMPANY CHILD AND THEIR FAMILY THROUGH CURE**

- Appropriate medicines for both the treatment of DS as well as MDR TB need to be available: child friendly formulations and FDCs
- NTP and other health care providers need to agree on who is responsible for treatment initiation. If done by other providers cases need to be reported to the programme
- Opportunity for NGOs, CBOs to engage in treatment support

Key stakeholders

- Global Policy makers
 - Provide policies, strategies and guidelines for the management of childhood TB based on best available evidence
 - Provide support mechanisms for these guidelines to be adopted at National level: training, technical support, monitoring and evaluation
 - Advocate for the conduct of nationwide surveys and strengthening of vital registration systems, to produce data to estimate the global burden of childhood TB
 - Count the number of children receiving preventive therapy
 - Define research needs for childhood TB
 - Include childhood TB in any policy considerations and decisions
- National policy makers/TB programmes
 - Ensure adoption, adaptation and implementation of childhood TB guidelines

- Nominate childhood TB focal point and create childhood TB working group at National level
- Provide training in childhood TB
- Include childhood TB in strategic plans and budgets
- Record and report childhood TB data according to WHO childhood TB guidance
- Support/perform operational research to improve childhood TB activities (See under 'Researchers')
- Collaborate with other maternal and child care services
- Collaborate with all providers caring for children and their families including pediatricians and private sector providers
- Related health care sectors
 1. Maternal and child care services
 - Exclude TB/diagnose/treat in pregnant women
 - Care for the newborn exposed to TB
 2. Facility-based child health services
 - TB as a differential diagnosis in children with respiratory symptoms and/or malnutrition
 - Recognize signs and symptoms of childhood TB – referral to TB services?
 3. Community child health services
 - Help to identify children with TB symptoms
 - Support case finding in the community
 - Support provision of preventive therapy
 - TB as a differential diagnosis in children with respiratory symptoms and/or malnutrition
 4. Educational/training institutions that provide pre-service training can incorporate child TB into training that is consistent with national guidelines and includes public health issues
 - Medical training curriculum
 - Nursing training curriculum
 - Public health training
 - Community health worker training curriculum etc
- Private care providers
 - Manage children according to national guidelines
 - Report children with TB to NTP
- CBOs/NGOs
 - Programme support (local): contact tracing, identification of children needing preventive therapy or referral for TB diagnosis, treatment support
 - Technical assistance
 - Training
 - Education & awareness

- Community
 - Education & awareness
 - Destigmatization
- Advocacy groups
 - Education & awareness

Shifting the paradigm to family and community-based strategies

Attention is now being focused on the importance of integrating diagnosis, treatment and prevention of childhood TB into maternal, neonatal and child health services where feasible/appropriate and the need for improved coordination and communication to provide a more comprehensive and effective service at the community level is being recognized. Shifting to this more family/community-centered approach will require effective collaboration and joint planning between programs responsible for TB control and maternal and child health services and initiatives aimed at expanding community-based prevention, screening and care. Improving TB services for mothers will be crucial to efforts to improve them for children. As much as possible, TB services for children should be “mainstreamed” into existing child health services. The most obvious approach is to integrate childhood TB services into programs where children with TB infection and disease are most likely to be seen, such as well-child care, malnutrition programs and centers for the care of children with HIV/AIDS.

While the exact mechanisms to include childhood TB services into other health sectors will vary, several widely distributed programs present clear opportunities for coordination and integration:

- *Integrated Management of Pregnancy and Child Health (IMPAC)*: Key interventions to improve maternal and newborn health that are delivered by health services, the community and the family are packaged as IMPAC. TB services, especially prevention and diagnosis should be considered core components at all stages of the program, including pregnancy, neonatal, postpartum and postnatal care. Such integration will reduce the associated maternal and child mortality and improve obstetrical outcomes.
- *Prevention of Mother-To-Child HIV Transmission (PMTCT)*: Screening for TB should be used to identify pregnant women living with HIV who are candidates for further diagnostic evaluation for TB disease, or for isoniazid preventive therapy. Earlier detection, treatment and prevention of TB will reduce the vertical transmission of HIV and the postnatal transmission of *M. tuberculosis*. Prevention of vertical transmission of HIV will facilitate the implementation of the integrated patient monitoring system of HIV (pre-ART and ART), PMTCT, and TB care recommended by WHO, the United Nations Children’s fund, and the Global fund to fight AIDS, TB and Malaria with standardized indicators.

- *Family planning and fertility services:* Tuberculosis diagnosis and prevention could be integrated into existing family planning services, and effective referral mechanisms should be established to enhance the diagnosis of TB among young women. Genital TB should be considered as an important cause of infertility in settings with high TB prevalence.
- *Integrated Management of Childhood Illnesses (IMCI):* IMCI is an integrated approach to child health that emphasizes the well-being of the whole child by reducing death, illness and disability while promoting growth and development among children < 5 years of age. The inclusion of TB diagnosis, treatment and prevention services has been lacking, and must be strengthened to stimulate health workers to properly suspect and detect TB early in the course, particularly in HIV-prevalent settings. Particular emphasis should be given to infants and children with clinical presentations of pneumonia, malnutrition and meningitis, especially if not responding to first-line recommended treatment.
- *Child malnutrition programs:* One of the major clinical diagnostic criteria for childhood TB is weight loss or malnutrition. Screening for TB should be a core activity for any malnutrition program in a setting with high TB prevalence.
- *Child HIV management programs:* Because of the intimate association between HIV and TB, it is crucial that programs established to manage children with HIV also have state-of-the-art programs to diagnose, treat and prevent TB. Effective efforts will require close communication and coordination between the TB and HIV/AIDS programs, with provision of adequate resources and expertise.

Implementation of TB services in these settings will be challenging as there is a dearth of operational research defining the optimal scope of services that should and can be provided. For each program, tools will be needed to prompt the health care worker to ascertain the information, ask the necessary follow-up questions and take the appropriate actions. This can be accomplished with tables, algorithms or “bundles” that will need to be validated in the setting. A bundle is a group of interventions that, when executed together, make a measureable improvement in clinical outcomes. The concept was developed mainly for quality programs but can be applied to other clinical situations. One strength of a bundle as a tool is in the measurement of completion of each element, and the action to which it leads. For a clinical program, the bundle is the package of activities related to a specific problem. For TB, depending on the clinical setting, this could include some or all from among: standardized questions about risk factors for recent exposure to an infectious case; history of TB testing and treatment; symptom review; tuberculin skin testing, if available; chest radiography for children; Sputum microscopy; Gene Xpert MTB/RIF; treatment of TB infection; treatment of drug-susceptible TB disease; evaluation and treatment of household members with IPT; and BCG vaccination.

Another set of groups that may be instrumental in the improvement of childhood TB services are non-governmental organizations (NGOs), community-based organizations (CBO's) and civil society

organizations (CSO'S). There are several critical areas of TB control that are a natural fit for these community-level efforts:

1. *Case finding:* Those providing many types of services can perform symptom screens for TB and link individuals with appropriate diagnostic services. This is most effective when based in the community, where people participate in their normal activities.
2. *Treatment support:* They can be instrumental in helping individuals take all their medications and attend their scheduled appointments. The traditional method of directly observed therapy where patients must report to a health care facility is unrealistic and impractical, and a common reason why people stop treatment before its completion. TB care can be crafted to fit patients' lives through community-based approaches.
3. *Community-level education and mobilization, including fighting stigma:* Behavioral change and social mobilization are often best organized by people and organizations that know and belong to the community. Many of these organizations have had excellent success with education for a variety of issues and health-related problems. They also can empower people with chronic diseases and are mindful of creating sustainable programs of support.
4. *Coalition building:* Many of these organizations have extensive knowledge of and experience in building coalitions among varied groups with a common interest. They can be instrumental in integrating maternal and child TB efforts into other programs, and creating the political will to do so. They often have skills in negotiation and many have existing relationships with national and local government leaders. They can help engage the natural partners for TB control within a community.
5. *Program monitoring:* Many have experience with program monitoring and measurement of program performance, efficiency and impact. This element often has been lacking from TB programs in general and childhood TB programs specifically.
6. *Training and supervision:* These organizations frequently provide assistance to increase local capacity for health-related programs. They can train their own staff and community workers, but also provide assistance to TB programs in certain specific areas. Joint training sessions with TB programs strengthen partnerships between the community and the TB program.
7. *Operations and Implementation Research:* Some of these organizations have extensive experience in designing, performing and evaluating new clinical operations and innovations. Some maintain databases, which can assist TB programs in evaluating their efforts. They have particular expertise in evaluating the effectiveness and community attitudes toward specific health care services.
8. *Advocacy, communications, and social mobilization:* These tools have generally been underutilized by TB programs, and they are often the hallmark of effective community-

based efforts. They can increase case detection, reporting of cases, knowledge of TB within a community, treatment adherence and success, and can reduce stigma. Utilizing these skills, they often can motivate change in the behaviors of both individuals and other organizations that have created barriers to effective TB control.

GETTING TO ZERO

There are several reasons why the study and control of childhood TB are important in all societies. The first is the disease burden and impact on the individual child and his/her family. TB can cause crippling disease in children, ending in either death or long-term disability. The resulting economic burden on the family and the community can be substantial. The second importance of childhood TB is as a public health measure of recent transmission of *M. tuberculosis* within a community. Those children who develop TB disease do so rapidly, usually within weeks to months after the initial infection has occurred. As a result, an accurate accounting of childhood TB is a sensitive indicator of the current rate of transmission of the organism in the community. The third issue is that many adults who develop infectious pulmonary TB were infected as children because the opportunity to detect and treat their infection was missed. Finally, there is the ethical and moral issue of diagnosing, treating and preventing TB in children. It is simply unacceptable for children to be excluded because their diagnosis and management may be more difficult or uncertain. Children must be included in the three pillars of public health: scientific research, policy development and the implementation of appropriate clinical practices.

WHO has recently outlined ambitious goals for post-2015 strategy and targets for TB prevention, treatment and care. The strategy is based on 3 pillars of innovative TB care; bold policies and supportive systems; intensified research and innovation. New targets are being set with recognition of the need for more country-specific solutions based on “knowing your epidemic”, prioritizing activities and targets accordingly.

This new strategy will highlight again on the one hand, the huge gap that child TB needs to fill. While new targets are being set in the wider TB control context, the lack of even baseline data for children makes the setting of targets for child TB impossible at this stage. On the other hand, the broadening of strategy from a traditional vertically-delivered, public health approach to include for example, engagement of community, civil society and private sector along with promotion of equity which will highlight “prevention” and “community engagement” provides huge potential opportunity for child TB.

Research Gaps

Research has an important role to play in the development, implementation and refinement of policies and programmatic interventions for the effective management and prevention of childhood TB although issues specific to children and the ways in which children and their families could be prioritized within the

global research agenda have not been well addressed historically. The newly published International Roadmap for TB Research, developed by the TB Research Movement and formally launched at the October 2011 conference of the International Union Against Tuberculosis and Lung Disease in Lille (France), presents priority research questions for six main areas with the aim to achieve TB elimination by 2050. Donald et. Al. have highlighted the key priorities for childhood TB in each of the six areas to be published shortly and these are outlined below (Donald et. al., An International Roadmap for Tuberculosis Research: Importance and Relevance for Child Health, in-press, 2012):

1. Epidemiology

- a. Better define the burden of disease among women and children including conducting nationwide inventory surveys to measure under-reporting of childhood TB
- b. Improve recording and reporting systems to capture and report data disaggregated by age and gender
- c. Improve the understanding of the variations in the dynamics of TB in different settings and the social, environmental and biological drivers of *M. tuberculosis* transmission in different settings

2. Fundamental research

- a. Characterize human TB by modern biochemical, clinical and epidemiological approaches and address issues specific to improving the understanding of TB in children
- b. Better understand the host-pathogen interaction including improved understanding in children of the ontogeny of the immune system in relation to its responses to mycobacterial infection at different ages
- c. Apply 'discovery science' to identify biomarkers that better differentiate the various stages of the disease spectrum and distinguish between infection and disease in children

3. Development of new diagnostics

- a. Evaluate recently introduced new diagnostics and determine their performance for confirming the diagnosis of TB in children
- b. Develop diagnostics suitable for pediatric samples
- c. Develop point of care diagnostic for (childhood) TB

4. Development of new drugs

- a. Identify optimal doses in children among new and existing anti-TB drugs and regimens
- b. Identify the optimal treatment duration and dosing of rifamycin-based treatment in children
- c. Identify aspects of the design of clinical trials specific to children as regards endpoints, sample size, inclusion criteria and at what point in drug development studies in children should be undertaken

5. Development of new vaccines

- a. Define suitable clinical endpoints & immunological read-outs for vaccine trials in children

- b. Improve clinical trials for vaccines in infants and children through the conduct of necessary pre-vaccine epidemiological studies, so as to standardize protocols, assays, methodological and clinical parameters, etc
- c. Develop improved vaccines for “prime-boost” vaccination that are safe and efficacious in the prevention of TB in children (including those with HIV and other immunosuppressing conditions) and define optimal conditions of use in children, including the definition of the best age periods for vaccination

6. Operational and public health research

- a. Strengthen recording and reporting; improve global estimates of childhood TB (DS and DR TB) including promotion of case-based electronic recording and reporting systems that would facilitate compilation and analysis of age-disaggregated data
- b. Best approaches for identification of exposed children and provision of preventive therapy
- c. Preventive therapy for children exposed to (M)DR TB
- d. Improve collaboration between TB and other child-care services for TB case finding and address specifically targeted childhood TB case-finding, screening, access to diagnostics, treatment access and delivery, TB/HIV programme interactions and infection control within the general context of health service and efforts to expand community-based care
 - i. How to improve implementation of collaborative TB and HIV activities in mother and child health?
 - ii. How can PMTCT programs be used to ensure appropriate TB screening of HIV-infected and uninfected women during pregnancy?
- e. Investigate how to optimise TB case finding in children and best measure the impact of intensive/enhanced case finding on mortality and other outcomes
- f. Determine the value of TB screening strategies in antenatal and HIV maternal/child programs
- g. Develop and evaluate models for how to implement sustainable collaboration with all private and public TB care and control providers
- h. How to implement sustainable collaboration with all private and public TB care and control providers.
- i. How are pregnant women and children being/will be addressed in the roll-out and scale-up of new diagnostic tests and new treatment and/or preventive regimens/options?
- j. What systems are in place/needed for monitoring and evaluation of these efforts?

Funding Gaps [section to be developed later]

Next Steps and Way Forward [section in-progress]

Improving childhood TB control will require many different strategies and activities. While improvements in basic TB control will be necessary, it is clear that enlisting the activities and resources of all relevant groups and programs that are dedicated to child health and survival will be equally important. Among the many steps to be taken are:

Short-Term (0 to 3 years)

- *Identify and engage key international and national stakeholders:* It is important to engage early the key stakeholders in child survival and children's services and link with TB control programme activities. We must develop policies and best practices that are compatible and consistent with existing programs for maternal and child health as well as TB programmes. This process has been started by having many organizations participate in the writing and review of this document.
- *Develop wider expertise based in TB endemic settings to support technical assistance and training in child TB* This is increasingly required with greater attention being given to child TB including as part of NTP reviews and TBTEAM.
- *Develop a framework for NTPs to support child TB activities*
- *Engage child health workers at all levels of care:* Childhood TB has not been addressed in an organized fashion by pediatricians/pediatric associations in many countries, even though child TB cases present and are managed by the child health services. Many cases including those managed in the private sector are not reported to the NTP. National child TB champions and national pediatric associations should show leadership and work with NTPs to educate pediatricians and other health workers about childhood TB, including the public health aspects, and to involve these health workers in development, implementation and monitoring of child TB activities.
- *Ensure that NTP guidelines include guidelines specific to infants and children that are evidence-based and relevant to specific national priorities and possibilities:* Currently, NTP guidelines of many countries lack sufficient detail about TB control in children. There is a standard set of issues that should be addressed, although the methodology and procedures will vary by country according to disease rates, resources and health systems. Each NTP should identify local resources and partners including non-governmental organisations that can aid this effort.
- *Improved reporting of childhood TB cases:* It is already recommended that every case of childhood TB should be registered with the NTP, and reported by age, disease type and treatment outcome. Standard WHO definitions at minimum should be used. NTPs may want to develop the means to provide additional data for monitoring and evaluation purposes. The NTP

need to work with child health services to improve the reporting of childhood TB cases including those cared for by the private sector.

- *Develop registers for contact screening and preventive therapy:* It is important to quantify the number of children eligible for and actually receiving preventive therapy to inform the need for increased resources including procurement and supply of preventive therapy. This should be a high priority for NTP and is already universally recommended.
- *Ensure availability of appropriate TB drugs for children.* There is a need for fixed-dose combinations that are appropriate for recommended dosages and that can be readily used for young children.
- *Ensure uninterrupted supply of quality TB drugs for children including for preventive therapy*
- *Operational research.* There is huge scope for operational research in child TB that could identify challenges and solutions to address the wide policy-practice gap, and improve the quality of child TB surveillance. Collaboration between national researchers and NTP should be encouraged to develop this capacity.
- *Clinical research.* Take the opportunity provided by increasing laboratory facilities in high burden settings to undertake research in children such as culture facilities (Global Laboratory Initiative) and GeneXpert
- *Begin to develop demonstration projects for inclusion of tuberculosis services into existing maternal and child health programs, such as IMCI, IMMCI, IMPAC and PMTCT:* A major theme of the child survival movement is integration of services. It is imperative that childhood TB be integrated into programs for maternal-child health, prenatal care, and disease management programs. However, it is not clear how to best achieve this, and the best practice may differ in various locales depending on the local structure of these programs. As the child survival roadmap that includes these programs will be developed largely at a country level, childhood TB needs to be “represented” within each country’s planning and implementation groups. Implementation and evaluation of demonstration projects will be a key activity to determining how to best incorporate tuberculosis services into the maternal-child health structure.
- *Form coalitions and partnerships to address specific aspects of childhood TB that cannot be readily addressed locally:* As an example, few areas even in high burden countries recognize and treat enough MDR-TB cases in children to be able to evaluate the best strategies for their management and prevention. However, the pooling of data and information from many sources will allow a more robust clinical and research agenda to be addressed. Some of these coalitions already have started, such as the Sentinel Project to address drug-resistant TB in children and these should co-ordinate with and contribute to regional GLCs.
- *Include child TB in the training curriculum.* Ensure that child TB management and important aspect of child TB control are part of any pre-service training such as for doctors, nurses, public health specialists and community health workers

- *Development of educational materials:* Comprehensive guidelines are extremely useful for some aspects of TB control, but likely will not be as useful for the TB non-experts we hope to engage. Multi-media educational materials are needed to engage pediatricians, policy makers, child survival experts, maternal-child health program managers and front-line workers, industry and funders.

Longer-Term (3-10 years)

- *Cost and cost benefit analyses of various aspects of childhood TB and potential strategies to improve management and prevention:* There have been few such analyses that could help drive evidence-based improvement and deployment of available resources for childhood TB. Conducting these studies will be crucial to influence government officials, industry, and funders of the value of investing resources into the management and prevention of childhood tuberculosis.
- *Work with industry, academia, major agencies, NGO's and other organizations involved in TB drug development to develop appropriate dosing schedules and child-appropriate and child-friendly formulations of new TB drugs:* Currently, much of the pharmacokinetic data that is necessary to determine optimal treatment of infants and children is gathered only after a new drug has been licensed, after Phase III testing. However, it is more appropriate to gather basic pharmacokinetic data for infants and children after completion of Phase II studies when the drug has been shown to be safe initially in adults. This will also allow for child-appropriate and child-friendly formulations of the medication to be developed as progress towards licensing ensues.
- *Improved diagnostics:* This is the most critical need in child TB. Improved diagnosis would lead to improvements in all aspects of clinical care and epidemiology. The need is more critical for children than adults because microscopy can identify the large majority of adult cases but only a minority of childhood cases. Improvements in diagnosis that might be considered insignificant for adults could represent a major improvement for children and should not be discarded before being evaluated in children.

List of Resources [in-progress -- section to be more fully developed later]

Guidance/guidelines

- WHO Childhood TB guidance (2006/2012)
- WHO Rapid Advice (2010)
- WHO/IUATLD TB/HIV guidance (2010)

Field guides

- Union desk guide
- Sentinel project: Field guide for the management of MDR in children (will be published in the fall)

Teaching/training tools

- WHO training tools (2012)
- MSF

Advocacy documents

- No more crying, no more dying
- MSF
- Sentinel Project: Being Brave (<http://sentinel-project.org/stories/>)
- Results brochure

Websites

- Stop TB Partnership (http://www.stoptb.org/wg/dots_expansion/childhoodtb/)
- WHO (<http://www.who.int/tb/challenges/children/en/index.html>)
- IUATLD (<http://www.theunion.org/index.php/en/what-we-do/child-lung-health-/childhood-tb>)
- CDC (<http://www.cdc.gov/tb/topic/populations/TBinChildren/default.htm>)
- Sentinel project on pediatric drug-resistant tuberculosis: <http://sentinel-project.org/>
- IMPAACT (<https://impaactgroup.org/>)
- Childhood TB subgroup of NDWG: <http://www0.sun.ac.za/NDWGChildTB/>
- Union working groups
- Childhood TB Task force of CORE group: <http://coregroup.org/our-technical-work/working-groups/tuberculosis>
- Pediatric TB Network in Europe (pTbNet): <http://www.tb-net.org/content/view/79/114/>
- www.childhoodtb.org

References

Appendices [TBD]