

TITLE:

TB in children, adolescents and women - continuing challenges

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Since tuberculosis (TB) was declared a ‘global emergency’ by the World Health Organisation (WHO) in 1993, the introduction of DOTS and DOTS-Plus strategies saved millions of lives.(1) However, the focus of these passive case finding strategies had little transmission impact and TB remains the leading infectious disease killer on the planet. Globally, of the 7 million new TB cases notified to the WHO in 2018, 58% were men (aged ≥ 15 years), 34% were women and 8% were children (aged < 15 years). (2) TB affects people of both sexes and in all age groups, with women accounting for 32% and children (aged < 15 years) for 11% of the estimated global burden.(2) While it is intriguing and important to consider the relative over-representation of men among TB cases,(3) we will focus on the challenges posed by children, adolescents and women to TB programs globally (Table 1).

Prevalence surveys to assess the TB disease burden usually exclude children less than 18 years of age, given concerns about study consent, cryptic presentations and poor diagnostic yield. As a result disease rates in children remain poorly quantified. However, it is recognised that children carry a huge TB disease burden, especially in areas with uncontrolled TB transmission, with more than 1 million children developing TB every year.(2) Furthermore, in TB endemic areas TB is a top ten cause of death in young children, yet it is frequently omitted from analyses of under-5 mortality.(4) The urgent need to improve TB prevention and care in children has been highlighted in the ‘Roadmap towards Ending TB in Children and Adolescents’ launched at the UN High level meeting on Ending TB in 2018,(5) but progress remains limited.

As childhood TB reflects recent *Mycobacterium tuberculosis* transmission, a critical strategy to protect children is to reduce ongoing transmission in the community. It is now appreciated that patients who are only mildly symptomatic, or even asymptomatic, may also be spreading TB.(6) A community-based active case finding intervention in Vietnam reduced TB prevalence by almost 10% per year and nearly halved TB infection rates among children.(7) A large proportion of cases diagnosed by using Xpert MTB/RIF® as a population screening test reported minimal symptoms. Apart from general socio-economic upliftment, only large scale community-level active case finding strategies have demonstrated the degree of epidemic impact required to meet ambitious End TB targets. These strategies are difficult and resource-intensive to implement at scale in high burden settings and more research is needed to identify the most effective and feasible strategies, consider the added value of treating TB infection together with active disease, and most importantly the long-term ‘return on investment’ given the high up-front costs compared to most interventions implemented to date in high TB incidence settings.

While children will indirectly benefit from success in driving down community TB transmission, this emphasis should not detract from the need to improve TB prevention and care in children. Poor infection control in health care facilities offers an example of how children may come to harm. Human immunodeficiency virus (HIV) services became acutely aware of the TB transmission danger posed by health care facilities, following documented nosocomial outbreaks of drug resistant TB. For children the danger is greatest where coughing adults and adolescents, who may have pulmonary TB, mix with vulnerable young children or those with immunocompromising conditions. This is a common occurrence in clinic waiting rooms when infants come for routine immunisations or weight checks. Newborn babies in multi-bed 'Kangaroo mother care units' are exceptionally vulnerable when coughing mothers or visitors are not adequately triaged.(8) Since TB disease presents months after hospital discharge, connection with the hospital exposure event is rarely made. Given that children with symptoms and signs suspicious of TB do not present to the TB programme, close interaction between maternal and child health services and private paediatricians is essential to reach these children.(9) In response to recommendations made in the 'Roadmap towards Ending TB in Children and Adolescents', WHO has supported high Tb incidence countries to develop their own child and adolescent TB action plans in order to identify adequately contextualised solutions that incorporate recent advances in child TB prevention, diagnosis and treatment.(10)

TB preventive therapy (TPT) is well established as an effective measure to prevent disease progression after documented TB exposure or infection. TPT is important to consider as a population based strategy to reduce the reservoir of infection from which future disease may arise,(12) including young children and people living with HIV. TPT scale-up within HIV programmes has been reasonable, but progress in the provision of TPT to young children following household TB exposure has been much slower, falling between the cracks of existing vertical programs. In 2018, only 349 487 children <5 years were initiated on TB preventive treatment, falling well short of the target of 4 million required during the years 2018-2022, as set out in the UN high-level meeting on TB declaration. Evidence suggests that most TB transmission occurs outside the household,(13) which may detract from the perceived value of treating infected TB contacts. However, household exposure still identifies an important high risk event especially for children and, given that TB services are already engaged with the family, it offers an excellent opportunity to protect children and limit epidemic spread. Pragmatic trials of feasible preventive therapy

implementation strategies in high incidence settings are urgently needed to close the persistent policy-practice gap.

Vulnerable young children also represent an important target group for new TB vaccines and novel approaches using existing vaccines. A lot remains to be discovered about the optimal use of bacillus Calmette Guerin (BCG), such as the best route of administration and strain-specific variability in the level of protection provided against TB and all-cause mortality. Recent studies in macaque monkeys suggest that intravenous administration profoundly alters the protective outcome, with more pronounced and durable immune stimulation as well as enhanced protection against disseminated disease, compared to more traditional routes.(14) Adolescents are another important target group for new vaccine-based prevention approaches. Repeat *Mycobacterium bovis* BCG vaccination is generally discouraged, but a recent study suggests that it may provide protection against TB infection in interferon-gamma release assay (IGRA) negative adolescents who received routine BCG vaccination at birth.(15) Unfortunately the study was not powered to measure protection against TB disease, but given BCG's availability and excellent safety profile, further exploration is warranted. Novel vaccines are also demonstrating enhanced protective efficacy and further developments are eagerly awaited.

Adolescents are an important group to consider given their contribution to TB transmission within the community and challenges with health care service engagement.(16) Current age categories for the reporting of TB data (<5years; 5-14 years, 15-24 years) do not allow differentiation of the adolescent group (broadly defined as 10-19 years of age), while prevalence surveys routinely exclude adolescents aged less than 18 years, despite the fact that they are able to expectorate sputum and develop adult-type TB disease that can be detected by traditional means. To improve the usefulness and accuracy of TB data in adolescents and young adults, programmatic data should be reported in 5-year age brackets for patients less than 25 years of age and children older than 10 years of age should be included in prevalence surveys. Adolescents require a special approach to optimise treatment adherence, especially in cases with drug resistant TB that require prolonged treatment. Specific challenges to consider include emerging autonomy, reduced perception of vulnerability, sensitivity to social stigma, and mental health issues including potential for drug addiction and peer pressure. Peer support groups have demonstrated a strong positive impact in HIV care,(17) but similar mechanisms for enhanced patient-centred care have yet to be employed in adolescents with TB.

It is generally expected that women are adequately represented in routine programmatic data and TB prevalence surveys, but this is not always the case. Access to routine diagnostic services and study participation may be limited in settings where cultural barriers restrict female autonomy and agency, while extra-pulmonary disease that is less readily detected in prevalence surveys is more common in women than in men.(18) In certain settings, older women are over-represented among TB cases,(2) which has relevance for children who are frequently cared for by their grandmothers. A specific group that is poorly represented in programmatic and research data is pregnant women, since pregnancy status is not recorded or reported in any surveillance data and pregnant women are routinely excluded from trials.(19) Immune changes related to pregnancy and the post-partum period may make women more vulnerable to TB disease progression, and recent data from Norway support this thesis.(20) However major knowledge gaps, regarding the impact of pregnancy on TB risk and the impact of TB disease and treatment on maternal and infant outcomes, remain. Considering routine reporting of pregnancy status and the creation of a large multicentre 'TB in pregnancy' register, similar to what was done in Norway, may present a good way forward to begin to close existing TB care gaps for pregnant women and other vulnerable groups.

Table 1. Continuing TB elimination challenges in children, adolescents and women

Group	Continuing challenges	Potential way forward
Children	<u>Prevention</u>	
	Implementing community-based active case finding strategies	Define optimal strategies and funding mechanisms to support this approach
	Effective airborne infection control in health care facilities	Adequate triage and isolation (or wearing of masks) of coughing adults and adolescents
	Optimal use of BCG and development of new improved TB vaccines	Identifying the optimal strain for, timing and route of BCG vaccination/re-vaccination; Continue to recognize the need for better TB vaccines with ongoing support for its development and testing
	Provision of preventive therapy to high risk contacts	Pragmatic implementation trials in high Tb incidence settings; Collect and report routine contact management data
	<u>Diagnosis and treatment</u>	
	Better integration of care	Create strong links between the TB program, paediatricians and MCH services
	Both under- and over-diagnosis	Context specific child TB training of all relevant health care workers
	Unnecessary treatment exposure	Trials to identify the shortest treatment duration necessary to effect cure
	Access to drug resistant TB treatment	Increased use of Xpert Ultra® to identify DR-TB in children; encourage treatment of “likely DR-TB” if recent close DR-TB contact.
Adolescents	Data quality	Report data in 5-year age bands; include children >10 years in prevalence surveys
	Health care engagement and treatment adherence	Provide adolescent friendly services and social support; learn from HIV
	Active case finding and contact screening	Active case finding in high-risk congregate settings; track and screen close contacts of infectious adolescent cases
Women	Cultural barriers to care	Support increased female autonomy
	Poor data on TB in pregnancy	Routine capture and reporting of pregnancy data; establish a dedicated ‘TB in pregnancy’ register
	<u>Prevention</u>	
	Provision of TPT to women of reproductive age who are latently infected.	Scale-up TPT of adolescents/women with HIV infection or recent TB exposure
	<u>Diagnosis and treatment</u>	
	Improve TB screening, diagnosis, and treatment outcomes in pregnant mothers and their infants	Create strong links between the TB program, women’s health care providers, and MCH services.

Develop TB training modules for all relevant health care workers who care for women of reproductive age, especially when pregnant. Integrate rapid TB screening diagnosis strategies in antenatal and postnatal clinics. Clinical and operational research to improve patient-centred care for pregnant women, with removal of barriers to inclusion of pregnant women in such research.

DR-TB - drug resistant TB; HIV - human immunodeficiency virus; MCH - maternal and child health; TB - tuberculosis; TPT - TB preventive therapy

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