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Progress and challenges in childhood tuberculosis

Published **Online** March 24, 2013 http://dx.doi.org/10.1016/S1473-3099(13)70031-8

The plight of children with tuberculosis is widely recognised and is increasingly becoming a priority for national tuberculosis control programmes. In 2012, WHO attempted for the first time to quantify the tuberculosis disease burden in children, estimating there to be 490 000 cases and 65 000 deaths in 2011.[1] Some limitations of this estimation were recognised within the WHO report[1] (table), such as the assumption that the ratio of notified to incident cases is the same for children and adults, even though under-reporting of child tuberculosis cases is very common. The estimated number of children with tuberculosis equates to less than 6% of all incident cases (8·7 million), whereas estimates from tuberculosis endemic areas suggest proportions of 10–15%.[2] Furthermore, tuberculosis-related deaths in children infected with HIV were classified as deaths due to HIV (not tuberculosis). Additionally, many children who die of common disorders such as severe pneumonia and malnutrition might have unrecognised tuberculosis.[3]

Unfortunately, child tuberculosis data reported by national tuberculosis control programmes are often incomplete and hampered by restricted diagnostic access in most tuberculosis endemic areas.[2] Children are frequently diagnosed in settings where the accuracy and quality of non-microbiological diagnoses is weak and

	Recent progress	Key challenges
Disease burden	WHO child TB factsheet 2012; formal estimates included in the WHO 2012 global TB report[1]	Estimates are highly conservative; poor quality of reported data; children excluded from planned prevalence surveys
Diagnosis		
Specimen collection	Proven feasibility of induced sputum, nasopharyngeal aspirates, and fine needle aspiration biopsy	Optimised use of stool samples and the so-called string test; enhanced concentration techniques for paucibacillary disease
MTB detection	Roll-out of fluorescence microscopy; roll-out of Xpert MTB/RIF assay	Fluorescence microscopy: insensitive to paucibacillary disease and cannot differentiate MTB from non-tuberculous mycobacteria. Xpert MTB/RIF: cartridge cost, limited availability, needs adequate specimens, and has suboptimal sensitivity in children
Treatment		
Drug-susceptible TB	New treatment guidance allows use of existing quality-assured paediatric formulations	Role of ethambutol is not well defined, not contained in fixed-dose combination preparations
Drug-resistant TB	Excellent outcomes possible in children with MDR-TB	Few children treated in existing MDR treatment programmes; substantial side-effects, especially ototoxicity with injectable use
TB–HIV co-infection	Expanded prevention of mother to child transmission programmes; early initiation of ART in all HIV-infected children	Role of ethambutol in all children with TB–HIV not well defined, adds to pill burden; need to consider ART adjustment when coadministrating protease inhibitors and rifampicin
Pharmacokinetics	Comprehensive pharmacokinetic data about first-line and second-line TB drugs in children are being collected	Data mostly coming from one geographic location
Prevention		
Infection control	Greater risk awareness and improved guidelines	Poor implementation in most TB endemic areas; frequent mixing of susceptible young children and coughing adults in waiting rooms
Preventive therapy	Pragmatic guidance using simple symptom-based screening	Massive policy–practice gaps; not included in monitoring and assessment activities; potential benefit of continuous isoniazid preventive therapy in infants exposed to HIV from TB endemic areas with suboptimal services remains unclear; safety and tolerability of new short-course preventive therapy options not yet known

TB=tuberculosis. MTB=*Mycobacterium tuberculosis*. RIF=rifampicin. MDR=multidrug-resistant. ART=antiretroviral therapy.

Table 1: **Recent progress and key challenges in childhood tuberculosis**

linkage with existing tuberculosis reporting systems is poor. Massive roll-out of the Xpert MTB/RIF assay might increase diagnostic yield[4] compared with sputum microscopy, but overall diagnostic yields remain low[5] and children are unlikely to be prioritised in settings where the early detection of drug-resistant tuberculosis is the key concern. Studies in a range of settings are needed to calculate the burden of tuberculosis and drug-resistant tuberculosis in children. The importance of linking tuberculosis prevention and care to maternal and child health programmes has been recognised, and more integrated approaches will be promoted in the future.[6]

Recent revision of recommended drug doses in children ended a period of prolonged uncertainty following recommendations that were not aligned with available quality assured paediatric formulations.[7] Expansion of the recommended isoniazid dose range from 10–15 mg/kg to 7–15 mg/kg will allow existing formulations with a 1:2 isoniazid-to-rifampicin ratio to be used without dose changes, greatly simplifying treatment before a more ideal formulation with a 2:3 isoniazid-to-rifampicin ratio becomes available. Despite pragmatic strategies and existing policies to provide preventive therapy to young children exposed to an infectious source case,[8] implementation is poor.[7,9] This problem is unlikely to improve unless the provision of preventive therapy, at least to the most susceptible children, is included in formal monitoring and assessment programmes.

Vaccination provides a highly effective strategy to control vaccine-preventable diseases; however, the fact that only a few people develop tuberculosis after *Mycobacterium tuberculosis* infection differentiates tuberculosis from classic vaccine-preventable diseases. More than 90% of immune-competent individuals seem to be inherently resistant to tuberculosis, which provides high levels of herd immunity at the community level (so-called natural herd immunity). The combined effect of known risk factors for tuberculosis, such as malnutrition, HIV infection, diabetes mellitus, cigarette and biofuel smoke exposure, chronic lung disease, and immunosuppressive drugs, reduces the protective effects of natural herd immunity to levels at which disease transmission can be sustained, particularly within susceptible subpopulations in the community.[10] Combined strategies that reduce the social determinants of disease and explore the protective value of vaccination strategies are needed to achieve ultimate tuberculosis control.

The BCG vaccine offers some protection against disseminated forms of tuberculosis in young children (and against leprosy), but does not consistently protect against adult-type tuberculosis.[11] Concerns about the safety of the BCG vaccine in HIV-infected children—especially the potential to increase HIV replication due to strong T-cell stimulation[12]—and disseminated BCG disease need careful consideration during genetically modified BCG vaccine development. Additionally, prominent T-cell epitopes are genetically highly conserved, similar to essential housekeeping genes, suggesting that *M tuberculosis* subverts some T-cell-mediated immune response to benefit its own survival and spread.[13] An accurate correlate or biomarker of protection has not yet been identified.[14] The important roles played by innate immune responses and localised (non-circulating) T-cell populations have only recently been described,[15,16] and these might lead to new discoveries. The diverse range of pathological abnormalities related to the ontogeny of the immune response in children[17] presents opportunities to characterise important immunological mechanisms. Immunohistological studies could also advance understanding of protective immune responses in children with latent *M tuberculosis* infection[18] and provide answers to many unresolved beliefs about latent tuberculosis infection.[19]

Improvements in the mechanistic understanding of tuberculosis disease and protection are greatly needed, as is a reduction in major policy–practice gaps, since most children in tuberculosis endemic areas are unable to access effective tuberculosis care.

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We declare that we have no conflicts of interest.

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Chasing Koch's chimera

On March 24, 1882, Robert Koch presented his findings on the discovery of the cause of tuberculosis to the Berlin Physiological Society.[1] This presentation was one of the most important in the history of bacteriology. The results set the ground rules of how to establish pathogenicity and led to the initiation of two approaches for tuberculosis control: vaccines and specific antituberculosis chemotherapy. Paul Ehrlich attended the meeting of the society and reasoned that if bacteria could be identified by specific stains, then they could be killed by the same means. In 1909, salvarsan was developed for the treatment of syphilis by Sahachiro Hata in Ehrlich's laboratory. Many years later in 1935, Ehrlich's disciple Gerhard Domagk produced the effective antibacterial dye prontosil.[2] Since the introduction of DOTS in 1995, a range of powerful drugs have led to the successful treatment of more than 51 million patients with tuberculosis.[3] Additionally, control of the disease by timely diagnosis followed by adequate treatment has led to a decrease in the number of people falling ill and dying from tuberculosis worldwide.[4]

Koch's commitment to turn his discovery into a practical method to eliminate tuberculosis worldwide led him to try to develop a new product that could treat tuberculosis. At the 10th International Congress of Medicine in Berlin in 1890, Koch announced that "if guinea pigs are treated they cannot be inoculated with tuberculosis and guinea pigs which already are in the late stages of the disease are completely cured, although the body suffers no ill effects from the treatment".[1] However, we now know that his discovery was not a vaccine for tuberculosis but tuberculin, which causes a potentially damaging hypersensitivity reaction.

A strong message of the 2012 World TB day was the need to rapidly develop vaccines for tuberculosis.[5] A vaccine is as appealing now as it was more than 120 years ago, and could make a substantial contribution to the elimination of tuberculosis. However, funding for tuberculosis control is under substantial pressure, and increased investment in vaccine development will cause resources to be redistributed. The development of a tuberculosis vaccine, far from being delayed by insufficent funding, is a high-risk and ambitious goal.