in living conditions and nutrition and availability of curative chemotherapy have led to worldwide death rates from tuberculosis falling to 18 per 100 000 in 2010.[3] Nevertheless, globally there were an estimated 8·7 million new cases of tuberculosis in 2011 and 1·4 million deaths,[4] with the greatest burden of disease falling in low-income and middle-income countries. The large number of people with multidrug-resistant tuberculosis is a particular concern—630 000 of 12 million prevalent cases in 2011.[4]

As new diagnostic tests, drugs, and drug regimens become available that have the potential to radically improve the detection and management of tuberculosis, the papers in the Series explore the challenges for successful implementation of these interventions. We are particularly grateful to Alimuddin Zumla and Marco Schito for proposing and guiding the Series, and to the many authors and peer reviewers for their contributions.

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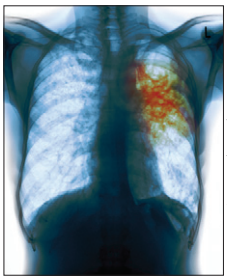

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Zero deaths from tuberculosis: progress, reality, and hope

Published **Online**
March 24, 2013
http://dx.doi.org/10.1016/S1473-3099(13)70039-2

See **Series** pages 349 and 362

See **Online/Series**
http://dx.doi.org/10.1016/S1473-3099(13)70015-X,
http://dx.doi.org/10.1016/S1473-3099(13)70025-2,
http://dx.doi.org/10.1016/S1473-3099(13)70030-6, and
http://dx.doi.org/10.1016/S1473-3099(13)70042-2

To commemorate World TB Day 2013, *The Lancet Infectious Diseases* is publishing a Series of articles on tuberculosis, a disease that has long plagued human beings and was declared a global emergency in 1993 by WHO. At that time, most *Mycobacterium tuberculosis* strains were susceptible to first-line tuberculosis drugs, and global control of the disease seemed a realistic goal. However, tuberculosis persists as one of the main causes of death from infectious disease: in 2011, 8·7 million incident cases causing 1·4 million deaths were estimated.[1] Roughly 630 000 cases of multidrug-resistant (MDR) tuberculosis occur worldwide, and extensively drug-resistant (XDR) tuberculosis is now reported in 84 countries.[1] Although the total global burden of tuberculosis is higher today than ever before, promising new diagnostic, drug, and vaccine pipelines provide hope for improved control of the disease.

In 2013, insufficient rapid, accurate point-of-care tuberculosis diagnostic tests, and the widespread unavailability of facilities to test for drug resistance, remain important impediments to global activities of tuberculosis control. In the first article of this Series, Stephen Lawn and colleagues[2] review recent advances in the development of new tuberculosis diagnostics. Although the Xpert MTB/RIF assay was rapidly endorsed by WHO in 2010 and is deemed a landmark diagnostic method, Lawn and colleagues point out the drawbacks and challenges facing the rapid roll-out of the assay in areas endemic for tuberculosis and HIV. Whether the test will accelerate progress towards the Millennium Development Goal of tuberculosis control targets is uncertain because many implementation issues could limit the effect of the Xpert MTB/RIF assay. Therefore, the urgent need for rapid, accurate, affordable, point-of-care tuberculosis diagnostic tests that are easy to use and implement remains a priority.

Accelerated antimicrobial development has created a range of promising new drugs and drug regimens against drug-sensitive and drug-resistant tuberculosis, which are now under clinical evaluation. Recent approval by the US Food and Drug Administration of delamanid for use in adults with MDR tuberculosis heralds the first new tuberculosis drug on the market since the introduction of rifampicin in the 1970s. Tuberculosis biomarkers are essential for accelerated development and assessment of these new drugs to capture the full effects of these interventions on clinical outcomes in many prospective, randomised clinical trials. In the second article of the Series, Robert Wallis and colleagues[3] look at the many *M tuberculosis* and human biomarkers. Despite recent scientific progress, discovery of accurate, clinically useful, prognostic biomarkers of tuberculosis remains elusive.

The increase in non-communicable diseases worldwide, and in particular in developing countries, now poses a competing factor on the unfinished agenda of communicable diseases in developing countries. In the third article of the Series, Ben Marais and colleagues[4] warn that a broad holistic approach to health-care

delivery is needed. The investigators point out major overlaps between non-communicable diseases and communicable diseases and justify improved integration of tuberculosis and HIV care with services for non-communicable diseases to enhance the efficiency of public-health services. In the present global economic recession, resources targeted for specific diseases through vertical funding streams need to be integrated more broadly across health-care systems. In the fourth article in the Series, William Wells and colleagues[5] recommend the prioritisation of rapid drug-susceptibility testing through improved delineation of molecular mechanisms of resistance and by the association of genetic polymorphisms with drug resistance. The authors discuss tuberculosis regimens, diagnostics, and drug-susceptibility testing and prioritise which future drugs to test, how to test them, and the development of new well characterised collections of *M tuberculosis* strains for the study of new drug-susceptibility testing assays. In low-income settings, surveillance data and modelling will help to design appropriate drug-susceptibility testing algorithms, assist in regimen change nationally, and clinical decision making for individual patients.

In the fifth article, Ibrahim Abubakar and colleagues[6] refer to the rising tide of MDR and XDR tuberculosis in eastern Europe, Asia, and Africa as a wake-up call for everybody, including governments of high-income countries. Most laboratories in countries with a high burden of tuberculosis are ill equipped to detect and diagnose the extent of drug resistance; therefore, most MDR tuberculosis and XDR tuberculosis cases are undocumented and unreported. As the history of tuberculosis in developed countries has shown, sustained investment in tuberculosis control and research programmes are needed to have a substantial and lasting effect. Abubakar and colleagues remind us of the urgent need for visionary political leadership to stop the rising tide of drug-resistant tuberculosis worldwide.

In the sixth article, Renaud Boulanger and colleagues[7] remind us that although a cure for tuberculosis has been available for many decades, the disease remains widespread, showing several human and structural failures. This paper addresses the role of community engagement in collaboration with relevant partners who share common goals and interests for tuberculosis control. Efforts to reinvigorate tuberculosis diagnostics, drugs, and vaccines worldwide are starting to bear fruit and provide hope for the achievement of global tuberculosis control targets. In view of the expected increase in demand for clinical trial sites in the coming years (as new tuberculosis diagnostics, drug regimens, and vaccines become available for clinical testing), research capacity needs to expand and local communities should get more actively involved in decision-making processes. Wider integration of tuberculosis-control activities presents opportunities to explore commonalities and potential synergies with other communicable and non-communicable disease services without the forfeit of recent gains or the compromise of functionality of existing tuberculosis and tuberculosis–HIV programmes. The need for sustained donor funding and increased political and financial commitment from governments of countries highy endemic for tuberculosis is greater than ever.

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We declare that we have no conflicts of interest. AZ receives support from the UCLH-NIHR-CBRC. AZ and MM receive support from the EDCTP and UBS Optimus Foundation. MS is funded by federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under contract number HHSN272200800014C. The opinions expressed herein are those of the authors and should not be construed as representing the official views of the US Department of Health and Human Services, or the authors' employers. The views do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organisations imply endorsement by the US Government.

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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**