Scaling up interventions to achieve global tuberculosis control: progress and new developments

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Tuberculosis is still one of the most important causes of death worldwide. The 2010 *Lancet* tuberculosis series provided a comprehensive overview of global control efforts and challenges. In this update we review recent progress. With improved control efforts, the world and most regions are on track to achieve the Millennium Development Goal of decreasing tuberculosis incidence by 2015, and the Stop TB Partnership target of halving 1990 mortality rates by 2015; the exception is Africa. Despite these advances, full scale-up of tuberculosis and HIV collaborative activities remains challenging and emerging drug-resistant tuberculosis is a major threat. Recognition of the effect that non-communicable diseases—such as smoking-related lung disease, diet-related diabetes mellitus, and alcohol and drug misuse—have on individual vulnerability, as well as the contribution of poor living conditions to community vulnerability, shows the need for multidisciplinary approaches. Several new diagnostic tests are being introduced in endemic countries and for the first time in 40 years a coordinated portfolio of promising new tuberculosis drugs exists. However, none of these advances offer easy solutions. Achievement of international tuberculosis control targets and maintenance of these gains needs optimum national health policies and services, with ongoing investment into new approaches and strategies. Despite growing funding in recent years, a serious shortfall persists. International and national financial uncertainty places gains at serious risk. Perseverance and renewed commitment are needed to achieve global control of tuberculosis, and ultimately, its elimination.

Introduction

Tuberculosis is a major global public health problem. Although substantial progress has been made, tuberculosis is still one of the most important infectious causes of morbidity and death in the world.[1] While the USA and most western European countries have reached record lows in tuberculosis rates and incidence is decreasing worldwide, the number of new cases in some metropolitan areas, such as London (UK), has doubled in the past 10 years.[2]

The 2010 *Lancet*'s Tuberculosis Series provided a comprehensive overview of global tuberculosis control and research efforts and challenges.[3] In this Review we provide a 2-year update, describe progress towards international targets, review important recent developments, and define key areas that hamper progress. We also emphasise the need to enhance strategic investments in areas that have enabled progress, and to intensify efforts to identify solutions for persistent difficulties. The global call to action is reiterated in view of current economic uncertainties.

Progress towards global targets

Progress towards global targets for tuberculosis control and improvements of estimates of the burden of disease caused by tuberculosis are discussed in detail in the WHO's latest global tuberculosis control report;[4] the most important findings are summarised here.

In 2010, an estimated 8·8 million (range 8·5 million to 9·2 million) incident cases of tuberculosis occurred, with 1·4 million deaths caused by tuberculosis. The highest incidences were in sub-Saharan Africa (figure 1), linked to the high prevalence of human immunodeficiency virus infection (figure 2). Global tuberculosis control targets are listed in the appendix, with progress towards these targets summarised in figure 3 and table 1. The latest estimate shows that global tuberculosis incidence has been decreasing by 1·3% per year since 2002, and the absolute number of incident cases has fallen since 2006. Incidence is decreasing in all WHO regions. Deaths from tuberculosis have fallen by 40% globally since 1990, and achievement of the 50% reduction target by 2015 is likely. Tuberculosis prevalence rates are also falling, but the target of halving 1990 rates by 2015 is unlikely to be achieved, except in the Americas and the Western Pacific region.

5·7 million new and recurrent tuberculosis cases were reported in 2010. This corresponds to two-thirds of all estimated cases, implying that about 3 million incident cases of tuberculosis were not reported and these patients likely failed to access proper care. Worldwide treatment success among reported tuberculosis patients reached 87% in 2009, the best ever recorded. However, treatment success remained worryingly low in the European region (67%), mainly as a result of the high prevalence of multidrug-resistant tuberculosis in the former Soviet republics. Overall, during the period 1995–2010, 7 million lives were saved[5] compared with what would have happened if pre-1995 care standards had remained unchanged.

Estimates of tuberculosis incidence, prevalence, and mortality continue to improve. The latest mortality estimates are based on direct measurements from national vital registration systems (in which causes of death are coded according to the international classification of diseases) and mortality surveys in 91 countries (including China and India for the first time)

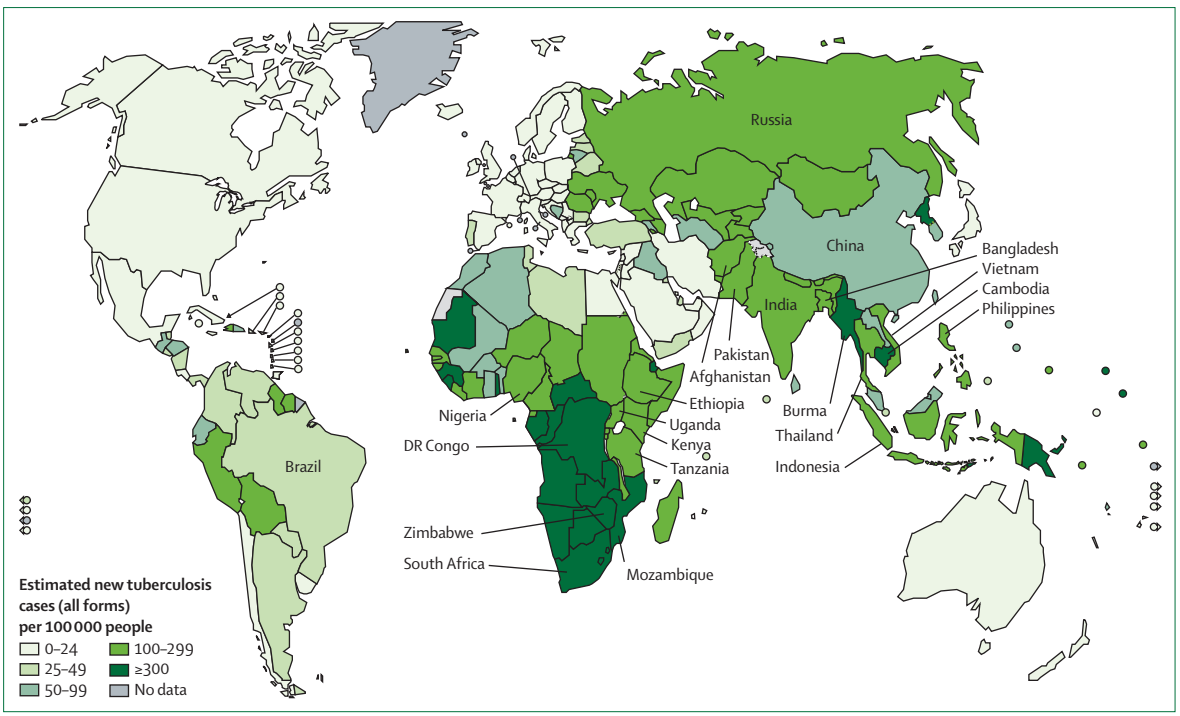

Figure 1: **Estimated tuberculosis incidence (2010)**
Data are from a WHO report.[4] The 22 countries with the highest burden of tuberculosis—which account for 80% cases worldwide—are labelled.

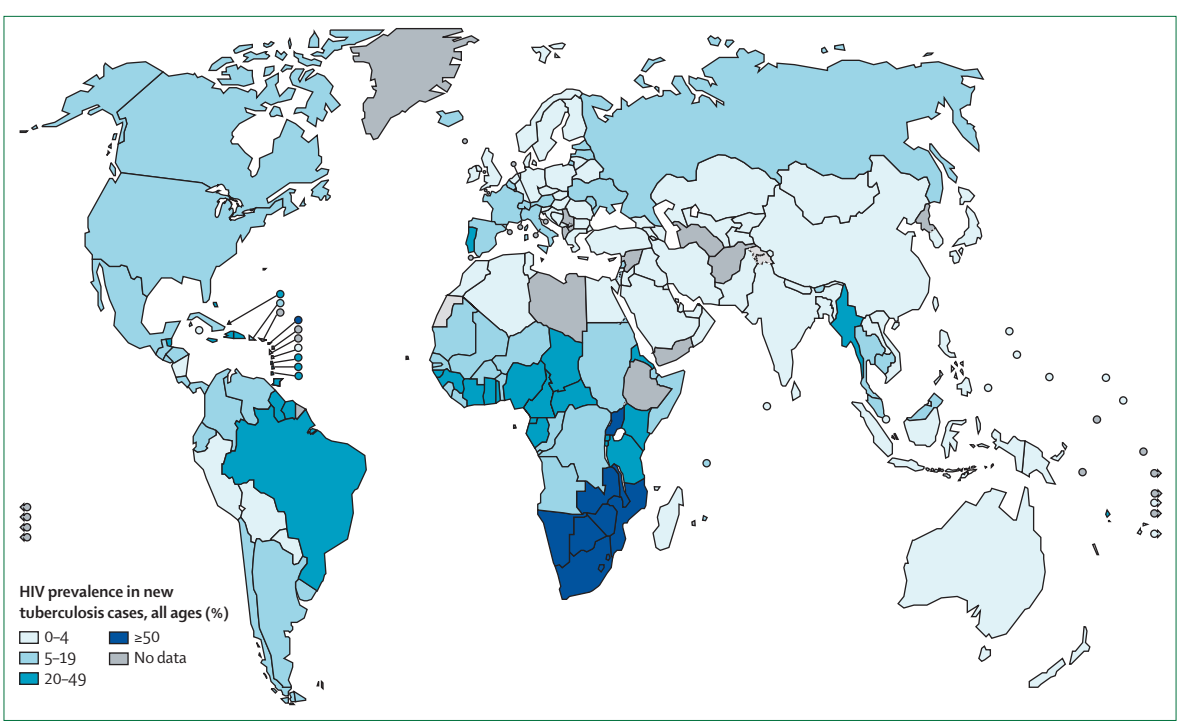

Figure 2: **Estimated HIV prevalence in new cases of tuberculosis (2010)**
Data are from a WHO report.[4]

that collectively account for 46% of all tuberculosis deaths worldwide. By contrast, before 2008, estimates of tuberculosis mortality were based on direct measurements in only three countries. In China, data from three national prevalence surveys (done in 1990, 2000, and 2010) showed that between 1990, and 2010, tuberculosis prevalence was

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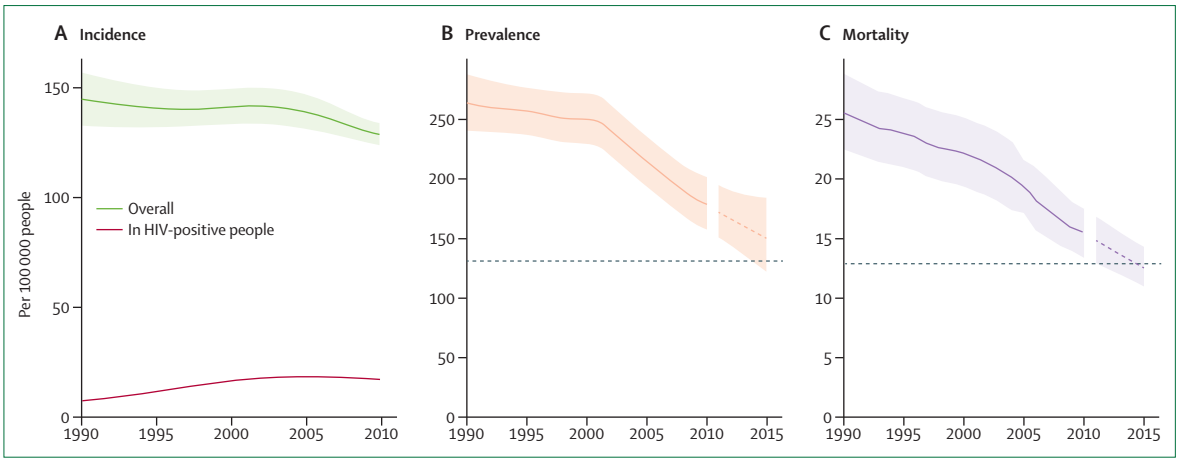

Figure 3: **Global trends in estimated rates of tuberculosis incidence, prevalence and mortality**
(A) shows global trends in estimated incidence of tuberculosis. (B) shows global trends in estimated tuberculosis prevalence (1990–2010) and forecast prevalence (2011–15). (C) shows mortality (1990–2010) and forecast mortality (2011–15). The dashed line is the Stop TB Partnership target of a 50% reduction in prevalence and mortality by 2015, compared with 1990. Shaded areas are uncertainty bands. Mortality excludes tuberculosis deaths in HIV-positive people.

	2010 incidence of tuberculosis (95% uncertainty intervals) and trend*	2010 prevalence of tuberculosis (95% uncertainty intervals) and change since 1990	2010 tuberculosis mortality (95% uncertainty intervals) and change since 1990	2010 estimated case detection rate (%; 95% uncertainty intervals)	2009 treatment success (%)
Africa	276 (256–296), falling 1·7% per year	332 (277–392), no change	30 (26–34), 17% decrease	60% (56–64)	81%
Americas	29 (27–30), falling 3·6% per year	36 (28–44), 61% decrease	2·2 (1·9–2·5), 71% decrease	80% (75–85)	76%
Eastern Mediterranean	109 (97–122), falling 0·7% per year	173 (112–246), 35% decrease	16 (12–20), 50% decrease	63% (56–71)	88%
Europe	47 (44–50), falling 1·8% per year	63 (47–80), 28% decrease	6·8 (5·4–8·3), 50% decrease	73% (68–78)	67%
Southeast Asia	193 (179–207), falling 1·1% per year	278 (206–360), 39% decrease	27 (21–35), 39% decrease	61% (57–66)	89%
Western Pacific	93 (85–107), falling 2·6% per year	139 (124–156), 44% decrease	7·5 (6·6–8·5), 63% decrease	79% (73–87)	93%
Worldwide	93 (85–102), falling 1·3% per year	178 (156–201), 32% decrease	15 (13–18), 40% decrease	65% (63–68)	87%

Data taken from the 2011 WHO global tuberculosis control report.[4] Full details of the methods used to produce these estimates of incidence, prevalence, and mortality, and case detection rates (defined as notifications of new cases plus relapse cases divided by estimated incidence) are provided in annex 1 of the report. Data are n per 100 000 people. Changes compared with 1990 are best estimates only. *Since 1990 (Americas, Western Pacific) or from the first year after 1990 that incidence started to fall (2002 worldwide, 1996 for Eastern Mediterranean, 2000 for Europe and Southeast Asia, and 2004 for Africa).

Table 1: **Progress towards global targets for tuberculosis control by WHO region between 1990 and 2010**

halved; additionally, new analysis of data from mortality surveys and a sample vital registration system show that mortality rates fell by almost 80% from 1990 to 2010. Ten national prevalence surveys will be completed in African and Asian countries in 2012 and 2013. In 2011, landmark achievements included the successful completion of a national prevalence survey in Ethiopia and a repeat survey in Cambodia to assess trends. Details of ongoing efforts to improve measurement of the tuberculosis disease burden via strengthened surveillance and prevalence surveys are available from the WHO Global Task Force on TB Impact Measurement.[6]

HIV-associated tuberculosis

Substantial progress has been made in collaborations to control tuberculosis and HIV.[4,7] Worldwide, the proportion of tuberculosis patients who knew their HIV status doubled between 2007 and 2010 (from 16% to 34%); in sub-Saharan Africa 876 918 of 1 475 117 (59%) tuberculosis patients knew their HIV status in 2010.[4] Almost 2·3 million of 3·9 million (60%) of people enrolled in HIV care during 2010 were screened for tuberculosis,[4] a four-times increase since 2007. However, despite recommendations that antiretroviral treatment should be started in all HIV-infected tuberculosis patients,[8] only 215 763 of 473 613 (46%) received antiretroviral treatment.

The optimum timing of initiation of antiretroviral treatment for tuberculosis patients diagnosed with HIV is now made on the basis of results from three randomised controlled trials—CAMELIA,[9] STRIDE,[10] and SAPIT[11]—which showed the safety and superiority of early initiation of antiretroviral treatment. Caution should be used for tuberculosis meningitis cases, for which early initiation of antiretroviral treatment has been associated with severe immune-mediated adverse events.[12] Rifabutin—the only rifamycin that does not adversely affect serum concentrations of protease

inhibitors used in second-line antiretroviral treatment regimens[13,14]—has recently been included in WHO's essential medicines list, although its availability is still restricted by high cost and it is not included in national essential drug lists in several countries.

A simple, symptom-based algorithm with high negative predictive value (97–99%) is recommended to exclude active tuberculosis in HIV-infected patients and identify those eligible for isoniazid preventive therapy,[15,16] including pregnant women.[17] Isoniazid preventive therapy reduces the risk of tuberculosis or death by 44–58%, mainly in patients with positive tuberculin skin tests.[18–20] Antiretroviral treatment has a substantial protective effect at both individual and population levels,[21] and tuberculosis protection is optimum when isoniazid preventive therapy and antiretroviral treatment are combined.[20,22] Despite convincing evidence and proof of good adherence in field studies,[20,23] isoniazid preventive therapy was given to only 178 144 of 1 464 579 (12%) eligible patients in 2010.[4] Important issues for combined tuberculosis and HIV programmatic and implementation research are summarised in the appendix. Two clinical trials are underway to assess empirical tuberculosis treatment in conjunction with antiretroviral treatment: REMEMBER (reducing early mortality and early morbidity by empiric tuberculosis treatment regimens; ClinicalTrials.gov number NCT00164281) and PROMPT (prevention of early mortality by presumptive tuberculosis treatment in HIV-infected patients initiating antiretroviral treatment; ClinicalTrials.gov number NCT01417988).

Drug-resistant tuberculosis

The emergence of drug-resistant tuberculosis is a major threat to global tuberculosis control.[4,24,25] Despite policy recommendations for diagnosis, infection control, and case management,[24–26] major structural, economic, and political constraints hamper control efforts.[27] To comprehensively assess global trends is difficult because laboratory facilities for drug susceptibility testing are insufficient in most countries with endemic tuberculosis. A survey done in Minsk (Belarus) reported multidrug-resistant tuberculosis in 55 of 156 (35·3%, 95% CI 27·7–42·8) new patients and 52 of 68 (76·5%, 66·1–86·8) previously treated;[28] the highest proportions ever reported and probably the worst case scenario resulting from previous poor management. The numbers of cases of multidrug-resistant tuberculosis officially reported to WHO rose from 29 000 in 2008, to 53 000 in 2010, but still represents only 18% of the estimated 290 000 (range 210 000–380 000) that could be detected if drug susceptibility testing was done in all notified tuberculosis cases.[4] This number of cases falls well short of targets set (figure 4). Furthermore, only 25% of the reported cases are treated according to WHO standards and since January 2010, the number of countries reporting extensively drug-resistant tuberculosis has risen from 58 to 77. These alarming data show the need for strategic deployment of new technologies and critical review of current strategies to assess whether they are helping or hurting.

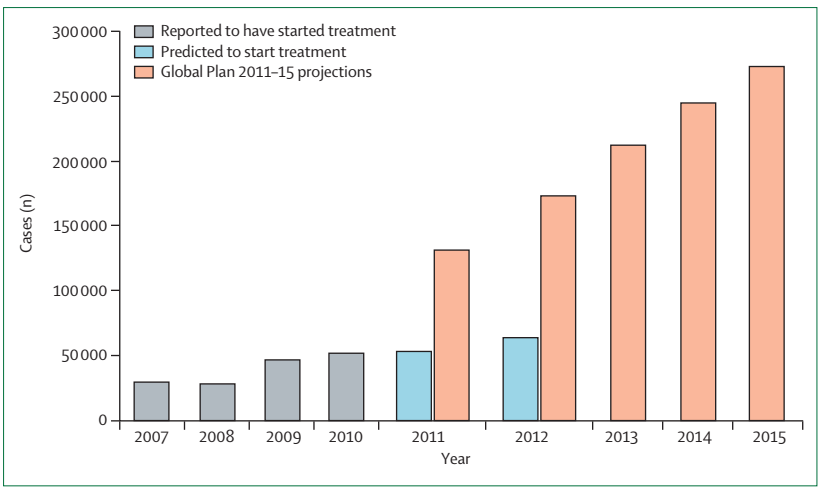

Figure 4: **Cases of multidrug-resistant tuberculosis reported and predicted, and Global Plan targets**
Total estimated number of cases of multidrug-resistant tuberculosis is 500 000, of which 300 000 occur in patients diagnosed with pulmonary tuberculosis.

Accurate diagnosis of drug-resistant tuberculosis is still a major bottleneck. In the European region 74 820 of 245 753 (30%) new cases and 34 272 of 61 626 (51%) of retreatment cases were tested for drug resistance 2010, and globally fewer than 95 569 of 5 417 772 (2%) new and 43 273 of 679 490 (6%) retreatment cases.[4,25] The Xpert MTB/RIF assay (Cepheid; Sunnyvale, CA, USA) and the Genotype MTBDRsl (Hain Lifescience, GmbH, Nehren, Germany) used in combination with the GenoType MTBDRplus assay (Hain Lifescience), enable rapid detection of drug-resistant tuberculosis.[29] Although worldwide roll-out of these new technologies has been constrained by cancellation of Global Fund Round 11,[30] implementation in many countries is progressing. A major concern is the potential widening disparity between access to diagnostics and treatment, because the capacity of well-supervised secondary treatment programmes is small.

Inappropriate tuberculosis treatment and fluoroquinolone use continue to drive the emergence of multidrug-resistant and extremely drug-resistant tuberculosis,[31] and the development of totally drug-resistant tuberculosis is a constant threat.[32] Measures to promote rational and responsible drug use include: enforcement of internationally recognised guidelines for management; enforcement of prescription-only use of tuberculosis drugs; promotion of education for the correct use of tuberculosis drugs; and reduction or elimination of any financial incentives that encourage irrational use.[33] Careful attention should be given to national treatment policies that might encourage increased resistance, especially if local drug resistance surveillance information is not available or is ignored.[34] Prompt

	Advances	Remaining challenges
Advocacy and awareness	European Centers for Diseases Control advocacy meeting, Stockholm, Sweden (February 2011) US National Institutes of Health meeting for diagnostic endpoints, Washington, USA (June 2011) Focus on children during World TB day 2012	Little national or regional advocacy in countries endemic for tuberculosis Identification and measurement of performance indicators
Disease burden	Good data for Europe and USA Repeat autopsy studies in progress (Zambia)	Poor reporting of age disaggregated data to WHO Establishment of accurate diagnosis in resource-limited settings
Diagnosis	Sputum induction possible on an outpatient basis Multicentre studies of Xpert MTB/RIF assay and other standardised platforms ongoing	Pragmatic options for collection of specimens Optimised processing of pauci-bacillary specimens Improvement of access to diagnostics in settings with limited resources
Treatment	Revised drug dose guidance for first-line tuberculosis drugs Paediatric development plans for new tuberculosis drugs	No child-friendly formulations meeting current recommendations Non-use of available drugs, because of diagnostic constraints Little safety and pharmacokinetic data for second-line tuberculosis drugs
Prevention	Greater emphasis on infection control in health-care facilities Universal recommendation for post-exposure isoniazid preventive therapy in vulnerable children	Few public health efforts to prevent community exposure and transmission Poor implementation of isoniazid preventive therapy strategies Few data for short-course preventive therapy options

Figure 6 shows advances in vaccine development.

Table 2: **Advances and remaining challenges in childhood tuberculosis**

diagnosis and appropriate treatment are essential to prevent the spread of drug-resistant tuberculosis within communities. New treatment guidelines[35] indicate the need to prescribe at least four drugs to which the strain is susceptible for at least 20 months, although the evidence is weak and more data for optimum case management is urgently needed, especially for extremely drug-resistant tuberculosis.

Tuberculosis in children

Maternal tuberculosis is associated with an increased risk of both tuberculosis and HIV transmission to infants,[36] while a study from Guinea-Bissau showed significantly higher all-cause mortality of children from tuberculosis households than those from households free of tuberculosis; eight-times higher if the mother had tuberculosis.[37] Accurate quantification of the global childhood tuberculosis disease burden is still problematic because accurate diagnosis is often difficult and many high-burden countries fail to report tuberculosis data disaggregated by age to WHO. Unfortunately, large prevalence surveys done to track progress towards Millennium Development Goals also exclude children. WHO estimates that 500 000 children develop tuberculosis yearly, resulting in around 70 000 deaths.[38] In Europe and the USA—where tuberculosis transmission is well controlled—less than 5% of reported cases occur in children,[39,40] but prevalence is highly variable, depending on immigrant status and country of origin.

Roll-out of the Xpert MTB/RIF assay offers opportunities to improve bacterial confirmation, with sensitivities of around 75% compared with culture from induced sputum[41] and slightly higher yields from lymph node aspiration biopsy samples.[42] The absence of a gold standard case definition and variable research methods has hampered diagnostics research in children. Expert workshops facilitated by the National Institutes of Health during 2011 produced international consensus on clinical case definitions and standard research methods for diagnostic studies.[43,44] Recent advances are summarised in table 2. Following a comprehensive review of published work WHO revised dose recommendations for first-line tuberculosis drugs in children,[45] but the absence of child-friendly formulations that meet these requirements is still a problem. Age-specific pharmacokinetic and safety data for second-line drugs have also been reviewed,[46] emphasising the need for more data and specific paediatric development plans for all new tuberculosis drugs.[47]

Infection control

Outbreaks of drug-resistant tuberculosis have re-emphasised the importance of infection control to restrict transmission in health-care facilities. A WHO policy document[48] for infection control defined the key principles and activities to be implemented, but there are major resource implications and no well-established system to monitor implementation. In a survey of 149 low-income and middle-income countries, 34 had done a national assessment and 45 had a national plan for tuberculosis infection control during 2010. An audit[49] of 200 tuberculosis patient records (150 with multidrug-resistant tuberculosis) in reference centres of five European countries identified infection control risks at each facility, especially the absence of negative pressure rooms. However, that only one case of tuberculosis occurred in health-care workers in 10 years shows the effectiveness of prudent administrative and personal protection measures.

Care provider and community involvement

Non-governmental and other civil society organisations galvanised massive support for HIV/AIDS and a similar movement is needed for tuberculosis. In many countries, universal access to quality-assured tuberculosis

diagnosis and treatment cannot be ensured without engagement of a wide range of public and private healthcare providers operating outside national programmes. However, many unlinked providers continue to diagnose and treat tuberculosis without oversight or an infrastructure to ensure good patient support and supervision.[50] Various public–private mix approaches have been adopted and scaled up, including incentive-based schemes for individual and institutional providers, social franchising, contracting out, and reimbursement for tuberculosis care delivered by private providers through health insurance when care conforms to agreed-upon standards. Creative community-based activities could also improve tuberculosis case detection and care.

In 2010, across 21 countries with adequate data, 20–40% of new tuberculosis cases presented to providers not traditionally affiliated with national tuberculosis programmes.[4] Estimated sales of tuberculosis drugs in the private sector were sufficient to treat an average of 66% of all new tuberculosis cases in ten high-burden countries assessed.[51] Some people with tuberculosis initially seek care from informal providers and pharmacies that often dispense antimicrobial drugs irrationally and of questionable quality. To address this, WHO and the International Pharmaceutical Federation issued a joint statement to initiate collaboration between national tuberculosis programmes and national pharmacy associations for pharmacists to identify and refer patients they suspect of having tuberculosis and, where possible, supervise tuberculosis treatment.[52] This statement now needs to be translated into action.

Progress in tuberculosis research

Progress in key areas related to diagnosis, treatment, and prevention, is outlined in the *International Roadmap for Tuberculosis Research*[53] published by the Stop TB Partnership and WHO in 2011, emphasising the need for ongoing investment across the full research spectrum from basic science to operational implementation.

Diagnostics and biomarkers

The most important advance in diagnostics was the excellent performance achieved by the Xpert MTB/RIF assay,[54,55] which has a user-friendly multifunctional platform. The assay also performs well in HIV-infected patients[56,57]—with a 45% increase in case detection compared with sputum smear microscopy—and can be used for diagnosis of extrapulmonary tuberculosis from a range of biological samples. The Xpert MTB/RIF Assay was rapidly endorsed by WHO in December 2010.[58] Concerns about false-positive rifampicin resistance results have been addressed by software revisions and redesign of one of the oligonucleotide probes, but WHO still recommends additional testing to confirm rifampicin resistance (especially in settings with low resistance), assess susceptibility to other drugs, and monitor treatment response. Cost and affordability is a major barrier. A concessional cartridge price of roughly US$16 has been negotiated for 145 eligible countries, which might be reduced to about $10 with further investment in the technology.

Other diagnostic tests endorsed by WHO and introduced in endemic countries in the past 2 years include molecular line probe assays for diagnosis of drug-resistant tuberculosis and a rapid *Mycobacterium tuberculosis* confirmation assay (Capilia TB-Neo; TAUNS Laboratories, Shizuoka, Japan).[30] Three non-commercial culture and drug susceptibility methods were endorsed: the colorimetric redox indicator method, the microscopic observation drug susceptibility assay, and the nitrate reductase assay.[59] Quality control is still crucial. Adequate external quality assurance for smear microscopy was

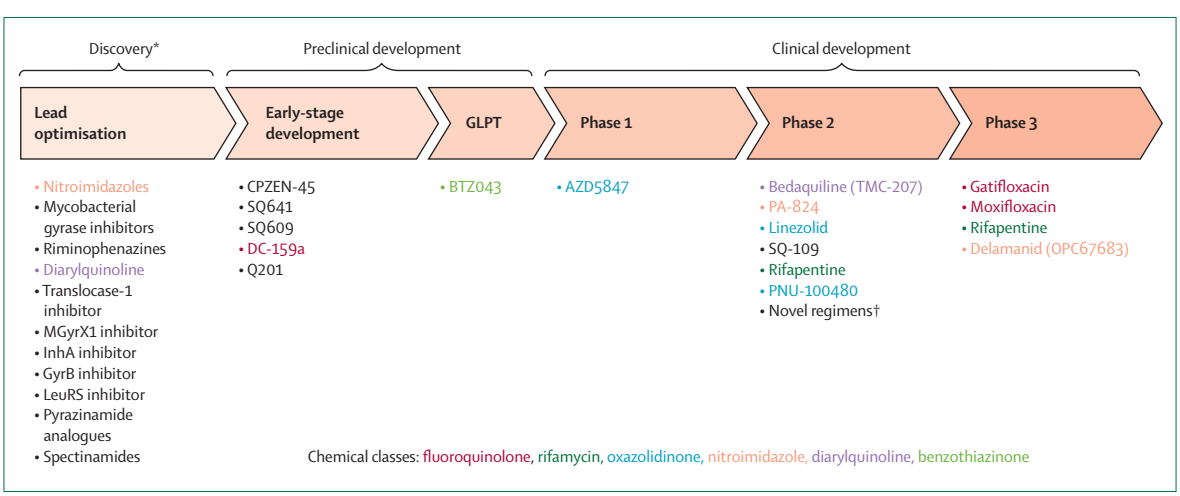

Figure 5: **Development pipeline for new tuberculosis drugs**
Source: Working Group on New Drugs, Stop TB Partnership. GLPT=good laboratory practice toxicology study. *Information for ongoing projects without a lead compound series are provided by the Working Group on New TB Drugs. †Combination regimens. The first clinical trial (NC001) of a novel tuberculosis drug regimen, testing the combination of PA-824, moxifloxacin, and pyrazinamide, was started November, 2010.

For more on **compounds in the discovery phase** see http://www.newtbdrugs.org/pipeline-discovery.php

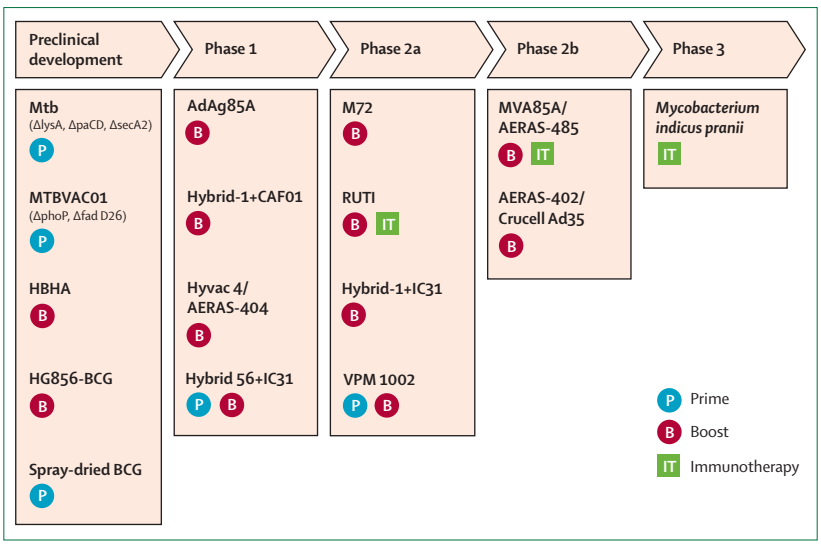

Figure 6: **Development pipeline for new tuberculosis vaccines (as of 2011)**
Data are from a WHO report,[4] personal communications (Peter Andersen and Ingrid Kromann; Bernd Eisele). The list of candidates in preclinical development is incomplete. Preclinical vaccine candidates are not yet in clinical trials, but some have been made with good manufacturing practice for clinical use and have undergone preclinical testing that meets regulatory standards. M72 is tested with AS01E adjuvant. *Mycobacterium vaccae*—originally developed for immunotherapy—has completed a phase 3 trial as a vaccine for HIV-infected Tanzanian adults.

documented in only 21 of 29 countries assessed in 2010,[4] but is expected to improve as part of the global laboratory strengthening initiative.[60]

Urine-based antigen assays are attractive as true point-of-care tests. Commercially available assays can detect mycobacterial lipoarabinomannan in urine, but have poor sensitivity.[61] Other diagnostic technologies in development include a breath analysis screening test and isothermal nucleic acid amplification assays.[30] In 2010, WHO issued an unprecedented negative policy guidance[59] about the worldwide use of commercial serological tests and indicated that the use of interferon γ release assays is not warranted in countries with endemic tuberculosis. European guidance recommends[62] that interferon γ release assays cannot replace standard methods for tuberculosis diagnosis, emphasising the inability of a positive test to differentiate tuberculosis disease from latent *M tuberculosis* infection, and the inability of a negative test to exclude active tuberculosis disease or latent infection in high-risk groups.

Progress in biomarker research[63] has lagged behind that of tuberculosis diagnostics. Preliminary evidence suggests that the proportion of tumour necrosis factor α *M tuberculosis*-specific CD4 T-cells might be used to distinguish tuberculosis disease from infection.[64] MHC class I and class II tetramer complexes allow direct visualisation of CD8+ and CD4+ T-cell responses against complexes of MHC and *M tuberculosis* peptide.[65] Gene and protein expression studies are a major focus of tuberculosis biomarker research,[66–68] although large overlaps in gene expression profiles show the importance of use of clinically relevant control groups.[69]

Drugs and treatment regimens

Although the tuberculosis drug pipeline is small, for the first time in 40 years, a coordinated portfolio of promising new compounds exists.[70] The development pipeline (figure 5) currently has ten new or repurposed drugs in clinical investigation.[70–72] Ongoing phase 3 trials are investigating whether treatment of drug-susceptible tuberculosis can be shortened to 4 months by substitution of gatifloxacin or moxifloxacin for ethambutol or isoniazid; results are expected from late 2013. Phase 3 trials are also assessing the ability of high-dose rifapentine to shorten treatment duration, given once or twice weekly with moxifloxacin, or daily, replacing rifampicin in the standard first-line regimen. For treatment of latent *M tuberculosis* infection in adults not infected with HIV, 12 weekly doses of supervised rifapentine and isoniazid had excellent outcomes.[73]

Two new drugs are in late phases of clinical development and are being tested in patients with multidrug-resistant tuberculosis: TMC-207 (bedaquiline) in a phase 2b trial and OPC-67683 (delamanid) in a phase 3 trial. Other compounds are in phase 2 trials, such as PA-824, linezolid, PNU-100480, and SQ-109. Clarification of the optimum use of these compounds in defined treatment combinations will need multiple trials.[70] Trials are lengthy and costly, since patients need to be followed up for an extended period to monitor for tuberculosis recurrence. Furthermore, existing tuberculosis treatment regimens have high success rates, which necessitate the use of non-inferiority trial designs for which large numbers of patients need to be enrolled. New approaches to trial design are urgently needed to speed up assessment,[74] such as the multigroup multistage trial design,[75] as well as increasing the capacity of sites in tuberculosis-endemic areas to implement trials. The Critical Path to TB Drug Regimens initiative[76] is a broad coalition of stakeholders that aims to accelerate the development of new treatment regimens with shorter therapy durations.

Vaccines

Tuberculosis vaccine research has made progress and several new vaccine candidates have emerged (figure 6),[77,78] but no major breakthroughs have occurred. A multistage subunit vaccine that combines canonical antigens (antigen 85B [Ag85B] and ESAT-6) with a latency-associated antigen (Rv2660) entered phase 1 clinical testing after showing pre-exposure and postexposure protective efficacy in mice.[78] Development of several vaccine candidates[79] has progressed; including the listeriolysin-expressing BCG construct (rBCGΔUreC:Hly), which has entered phase 2a, and the viral-vectored booster vaccines MVA85A/Aeras-485 and Crucell Ad35/Aeras-402, which entered phase 2b in 2011. Unexpectedly, the Oxford MVA85A/Aeras-485 vaccine had reduced immunogenicity when administered within the expanded programme of immunisation,[80] showing the multitude of effects to consider. Further development of the modified BCG-based

vaccine Aeras-422 (recombinant BCG expressing perfringolysin as well as Ag85A, Ag85B, and Rv3407) was halted when two phase 1 study participants developed shingles, most likely through reactivation of dormant herpes virus after vaccination. In the absence of any useful biomarker of protection, rational prioritisation of vaccine candidates is difficult and unbiased gating criteria are urgently needed to ensure that the most promising vaccine candidates are developed as rapidly as possible.[81]

Basic science

Surprisingly, in view of the intimate relation between *M tuberculosis* and the human immune system, the major antigenic proteins are highly conserved, suggesting that *M tuberculosis* might benefit from recognition by human T cells.[82] However, this observation might be an oversimplification, since comparative gene expression studies[83] of clinical isolates show lineage-specific transcription patterns in response to host-derived stimuli and genetic variation within the immunodominant Esx family has been reported.[84] The modern lineages (including the Beijing family) that evolved in high-density populations induce substantially less early inflammatory responses than do isolates belonging to ancient lineages, at least in mice,[85] which might be relevant to vaccine development.

The fruits of basic research usually take several years to reach the translational stage, and sometimes this step occurs by serendipity. 60 years after the discovery of pyrazinamide, its real target has been discovered.[86] This knowledge could enable rational development of more potent inhibitors of the RpsA–tmRNA system. Target-based approaches to tuberculosis drug discovery have been disappointing, but a simple model has been established for testing drugs against non-replicating bacilli that is operational both in vitro and in animal models.[87] New systems have also been developed to assess the vulnerability of targets by controlling gene expression with inducible promoters[88] or by tagging the corresponding protein genetically, thus rendering it less stable.[89] Such an inducible degradation system was used to assess the vulnerability of known tuberculosis drug targets in *Mycobacterium smegmatis* by establishing the threshold for inhibition.[90] Inducible depletion is an attractive new method for validation of drug targets and the system should be used for *M tuberculosis*.

Operational and implementation research

Although new drugs, treatment regimens, and vaccines are eagerly awaited, achievement of the 2015 international targets for tuberculosis control depends crucially on better use of currently available methods and resources by national programmes.[53,91] Unfortunately, few programmes have integrated operational and implementation research with their routine activities, which might be a result of a failure to appreciate the value of such research, insufficient research capacity, and weak links with national or international research institutions.[92] *Priorities in Operational Research to Improve TB Care and Control*[93] identifies research priorities in five major areas: access, screening, and diagnosis of drug-susceptible and drug-resistant tuberculosis, development of sustainable collaboration with all practitioners for tuberculosis care and control, prevention and treatment of tuberculosis in HIV-infected patients, optimum access to and delivery of treatment and retreatment of drug-susceptible and drug-resistant tuberculosis, and capacity building. It provides programme managers with methods for addressing policy questions to develop locally relevant evidence for optimisation of services.

New approaches to increase case detection

Increasing early detection of tuberculosis has the potential to improve individual outcomes and reduce transmission within communities. Although improved diagnostics will increase tuberculosis detection in patients accessing health services with symptoms and signs of active tuberculosis, many patients have few symptoms, and thus do not fulfil definitions of suspected tuberculosis, or cannot reach the appropriate health services because of barriers to access. Prevalence surveys of areas endemic for tuberculosis show that 50–60% of people with culture-confirmed tuberculosis do not report chronic cough, and 15–25% report no symptoms.[94] Classic tuberculosis symptoms also occur less frequently in people with HIV,[95] and in children and women, and might be masked in pregnancy. Thus, a large proportion of patients with active tuberculosis will go undiagnosed if only passive case detection is used.

More active approaches are needed to increase case detection, as proposed in the newly developed *European Union Standards for TB Care*.[96] Tuberculosis screening should target poor, vulnerable, and disadvantaged people with substantially increased risks of tuberculosis,[97] including people with HIV/AIDS, the homeless, slum dwellers, refugees, illegal migrants, alcoholics, people who misuse substances, prisoners, miners, health workers, people taking immunosuppressive drugs, and people with cancer or malnutrition.[97,98] A study in Zimbabwe[99] showed that mobile sputum collection vans deployed in high incidence areas improved access to tuberculosis diagnosis and treatment. WHO is preparing guidelines for active case detection on the basis of systematic reviews, which will be published in 2012.

Non-communicable diseases and tuberculosis

Non-communicable diseases—smoking-related and occupational lung disease, diet-related diabetes mellitus, and alcohol and drug misuse—are important risk factors for tuberculosis at a population level[97,98] and cross-programme links need to be strengthened.[100] The Tuberculosis and Tobacco framework, the Practical Approach to Lung Health guidelines, and the tuberculosis and diabetes

framework,[101,102] recommend bi-directional screening and actions to improve health behaviour of tuberculosis patients. Efforts to improve diagnosis and management of non-communicable diseases within strengthened primary health care also offer ways to improve tuberculosis control.[103] However, even broader collaborations are needed to address food insecurity and poor living conditions, which drive tuberculosis across the world. Actions to address these social determinants are needed from outside the health sector, as described by the Rio Political Declaration on Social Determinants of Health, in October 2011.[104] Global health and tuberculosis control experts should actively engage in shaping this holistic agenda.[105]

Financing and funding

Funding for tuberculosis control reached $4·2 billion in 2011,[4] with domestic sources accounting for $3·6 billion (86% of total funding) and the Global Fund contributing $0·5 billion (82% of all external funding). Despite increased funding in recent years, funding gaps remain large—$1·2 billion in 2011, and $2 billion in 2012—compared with the requirements stated in the Global Plan to Stop TB 2011–2015.[106] Funding gaps especially constrain scale-up of services for multidrug-resistant tuberculosis. Funding for tuberculosis research was $617 million in 2010, down from $619 million in 2009,[4] and only a third of the estimated need of about $2 billion per year.[107] External funding for tuberculosis ($0·6 billion in 2011) continues to fall far short of funding for HIV ($6·9 billion in 2010) and malaria ($2·0 billion in 2011).

Huge variability in domestic spending exists among the 22 countries with the highest burden (figure 1), which account for 80% of tuberculosis cases worldwide. In 2010, Brazil, Russia, India, China, and South Africa were 95% self-funded, but the other 17 high burden countries were highly dependent on Global Fund grants and only 51% of funding was from domestic sources.[4] Therefore, the ongoing financial difficulties faced by the Global Fund are a major threat to gains in tuberculosis control.[30] With economic stagnation in traditional donor countries and the associated cancellation of any new round of funding by the Global Fund until 2014, securing sufficient funding for tuberculosis control and scale-up of activities to combat drug-resistant tuberculosis will require increased domestic funding and access of previously untapped external resources.

Conclusions and reiteration of the call to action

Progress is evident, but the path towards tuberculosis elimination remains long, arduous, and challenging. The large case detection gap shows the inadequacies of health services that are either poorly functional, inaccessible to patients, or failing to capture all active cases early enough to reduce transmission. HIV-associated tuberculosis still presents a formidable challenge, especially in sub-Saharan Africa, as does the continued threat of drug-resistant tuberculosis. Improved care of children depends on the scale-up of tuberculosis prevention, improved diagnostics, and the availability of appropriate child friendly fixed-dose combination tablets. Issues such as infection control, meaningful engagement of all care providers, and community involvement are only now starting to be addressed in many settings.

Sustained improvement in global tuberculosis control requires strong and ongoing support across the continuum from basic science to operational research and implementation. Bridging the financing gap remains a major issue, despite the proven cost-effectiveness of tuberculosis interventions and the millions of lives saved. The previous call to action to all stakeholders is reiterated,[3] since even more commitment from governments, non-governmental, and other civil society organisations, and donors, is needed to pursue global control of tuberculosis and, ultimately, its elimination.

Contributors

AZ, BM and MR initiated and coordinated the Review, and wrote the first and final drafts. All authors contributed to the writing of the Review.

Conflicts of interest

SHEK is a co-inventor of the tuberculosis vaccine VPM 1002. All other authors declare that they have no conflicts of interest.

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