Since 1990, progress has been made toward global tuberculosis (TB) control, as measured by targets set for 2015. However, TB remains a major threat to health around the world. In 2013, there were an estimated 11 million prevalent cases, and an estimated 9.0 million incident cases occurred globally. Approximately 1.5 million deaths were caused by TB, including 360 000 among people living with HIV. Substantial challenges threaten future control efforts. These include multidrug-resistant forms and co-infection with HIV, as well as other factors, such as the increased prominence of noncommunicable diseases and adverse socioeconomic conditions. Beyond 2015, TB control must be seen as both a public health imperative unto itself and a vital component of economic development plans. To that end, control strategies should exploit technical and operational innovations to improve TB control and care and should promote universal health coverage and social protection mechanisms to expand access to essential prevention, diagnostics, and treatment services while avoiding catastrophic costs incurred by patients.

**After 1990: The Road to the 2015 Policies and Targets**

Since 1990, several key events have shifted global strategies to control TB, and global epidemiology has also changed (Figure 1). In 1991, the World Health Assembly set global targets for 2000 (3), with a model-based goal of reducing prevalence and incidence by 5% to 10% annually (4, 5). Targets were based on the assumption that achieving a 85% cure rate and 70% case detection rate would reduce prevalence of active TB cases, thus leading to reduced transmission and the overall burden of illness and death (6, 7). To further increase international attention and political commitment, the World Health Organization (WHO) declared a “global tuberculosis emergency” in 1993 (8). The next year, WHO announced a new strategy focused on bacteriologic detection among persons spontaneously presenting with symptoms to health service points and the provision of standardized short-course chemotherapy. In 1995, this strategy was branded as DOTS (directly observed treatment, short-course) (9, 10). After initial positive results from China and elsewhere (11), the strategy was promoted aggressively worldwide, although a lack of funding and political commitment were major barriers for its adoption at the country level.

Recognizing the growing number of TB organizations at all levels, as well as its own financial constraints (12), WHO convened an ad hoc committee in London in 1998 (13). The event was a watershed moment toward more collaborative partnerships and coordinated global action. Since then, established health organizations (such as WHO, the International Union Against Tuberculosis and Lung Disease, the U.S. Centers for Disease Control and Prevention, and the KNCV [Koninklijke Nederlandse Chemische Vereniging] Tuberculosis Foundation) were joined by many bilateral organizations, private companies, nongovernment organizations, and newly formed research and funding institutions (including the Bill & Melinda Gates Foundation and the Global Fund to Fight AIDS, Tuberculosis and Malaria [Global Fund]). Formally founded in 2001, the Stop TB Partnership has served as a platform to facilitate collaboration among these organizations.

**Tuberculosis (TB) remains a major health threat around the world. In 2013, an estimated 11 million prevalent cases (that is, the number of cases in a population at any given time) and 9.0 million incident cases (that is, the number of new cases that occur in a population in 1 year) occurred globally.** (1) Of the estimated cases, 3.3 million were missed by health systems, either by remaining undiagnosed or by being diagnosed but not reported (1). In the same year, an estimated 480 000 new cases of multidrug-resistant (MDR) TB, defined as resistance to both isoniazid and rifampicin, emerged, but only 136 000 were diagnosed and notified (1). An estimated 1.1 million incident cases occurred among people living with HIV, 550 000 occurred among children, and 3.3 million occurred among women (1). Approximately 1.5 million deaths were caused by TB worldwide, of which 210 000 were due to MDR TB and 360 000 were among people living with HIV (1).

Despite the continued severity of the epidemic, progress has been made in global TB control since 1990: The absolute number of cases globally declined at an average rate of 1.5% per year from 2000 to 2013 and 0.6% between 2012 and 2013 (1, 2). Countries have prioritized TB control by implementing internationally recommended strategies, increasing domestic funding, and incorporating TB into development agendas. Community-based organizations and other local groups have played an increasingly important role in TB care and prevention, aiding in providing comprehensive patient services.

In this article, we review the progress toward the 2015 TB global targets since 1990 (Appendix, available at www.annals.org). We detail current challenges to control efforts, including MDR TB and co-infection with HIV and TB, as well as broader socioeconomic issues. Beyond 2015, control strategies should quickly implement technical and operational innovations, as well as promote universal health care to improve access to services and avoid catastrophic expenditures.
Two important milestones occurred in 2000. In March, a ministerial conference held in Amsterdam sought to expand the global implementation of the DOTS strategy (14), and by year end, 148 countries had committed to scaling up the strategy (9, 15). In September, the United Nations Millennium Summit incorporated TB targets into the Millennium Development Goals, with 2015 set as the target year (16). After waning international interest in the 1970s and 1980s (10), TB moved back onto the global agenda during the 1990s. By the early 2000s, the Millennium Development Goal to halt and reverse the global incidence of TB was achieved.

In 2006, the Stop TB Strategy was launched as an enhancement of DOTS, in line with a broader push toward the Millennium Development Goals (17, 18). The strategy explicitly addressed MDR TB and co-infection with HIV and TB while also promoting public-private mixed approaches and community engagement. After a 2009 ministerial meeting of the 27 countries with a high burden of MDR and extensively drug-resistant TB, drug resistance became a global priority, as galvanized by a World Health Assembly resolution (19, 20).

Substantial gains have been made in TB research and development (21). New molecular diagnostics, such as the Xpert MTB/RIF (Cepheid) or GenoType MTBDplus assay (Hain Lifescience), have been introduced, and existing funding mechanisms, such as the Global Fund and UNITAID, have allowed for the deployment of new diagnostics in complex, low-resource settings (22). Two new medicines, bedaquiline and delamanid, have gained conditional approval for use in MDR TB cases, and 16 new vaccine candidates are at various stages of clinical trials (23–27).

Global TB prevalence, incidence, and mortality rates have been declining since the early 2000s (Figure 2). New treatment options have been explored, with varying success (28, 29). Moving forward, control strat-
Strategies must address social and economic determinants of disease, be integrated into development agendas, and promote universal health coverage as a means to mitigate barriers to accessing services (30). In 2014, the 67th World Health Assembly approved the WHO End TB Strategy, 2016–2035, which encapsulates broader approaches toward ending the TB epidemic as a major challenge to public health (31). Although the assessment of the epidemiologic effect of policy shifts is not an easy task, given that economic improvements contribute to reducing the burden of TB, robust control measures since 1990 have been concomitant to progress in epidemiologic indicators toward the 2015 targets.

### Reaching the 2015 Targets

Recent retrospective analysis estimates that overall TB mortality rates (not including people living with HIV) decreased from 30 cases per 100 000 persons in 1990 to 20 cases per 100 000 persons in 2009 (4). From 2000 to 2013, approximately 37 million lives were saved by TB prevention, diagnostic, and treatment interventions (1). Increased funding has been pivotal. Total domestic and international donor TB funding in 104 low- and middle-income countries increased from $1.7 billion in 2002 to $4.4 billion in 2011, and domestic funding alone increased from $1.5 to $3.9 billion over this period (32). The Global Fund is the largest provider of international donor funding, disbursing $500 million in 2012 (1).

Although progress has been substantial, major challenges remain (Figure 3). At the present rates, the goals of decreasing global prevalence by half by 2015 will not be met. Of the 22 designated high-burden countries, incidence is not yet decreasing in 7, 11 are
unlikely to reduce the mortality rate from 1990 levels by half, and another 11 are unlikely to reduce the prevalence from 1990 levels by half (1). To reach the ultimate goal of eliminating TB by 2050 (defined as ≤1 case per 1 million persons), incidence rates must decrease by an average of 20% annually, a rate of decline that has never been empirically achieved (26). New technology and more effective service delivery are thus required to accelerate the decline toward elimination and confront challenges, such as co-infection with HIV and diabetes.

**Drug-Resistant TB**

Drug-resistant TB presents a complex and evolving challenge to future control efforts. It often indicates weak implementation of TB care and poor infection control practices to prevent transmission once it is created (5, 33–35). Drug resistance emerges out of mutations that are selected or caused through the inadequate or inappropriate use of drugs (24). Drug resistance can also rarely develop in the absence of therapeutic errors, even with excellent patient adherence and proper supervision, because of poor quality of drugs or selective defects in absorption (36). Transmission by infectious patients to others further increases the spread of drug resistance (33, 37), particularly in congregate settings (24, 38), as well as in HIV-prevalent contexts (39).

Drug resistance varies greatly globally, with the highest reported proportion among new and previously treated cases found in Eastern Europe and Central Asia, whereas India and China have the largest absolute burdens (1). By 2013, 100 countries reported at least 1 case of extensively drug-resistant TB (1).

Diagnosing drug resistance at or near the point of care continues to pose difficulties (40, 41). The problem is in part due to the absence of a simple diagnostic tool and the low implementation of existing first-line drug sensitivity testing, administered in 2013 to only 8.5% of new bacteriologically confirmed TB cases and 17% of previously treated cases reported to WHO (1). In 2010, WHO endorsed the use of Xpert MTB/RIF; by the end of September 2014, more than 17,000 modules and 8.8 million Xpert MTB/RIF cartridges had been rolled out in 110 countries (42). This resulted in 136,412 MDR TB cases or presumed MDR TB cases (rifampicin-resistant cases detected by Xpert MTB/RIF) being reported to WHO in 2013, representing a 47% increase compared with 2010 (1).

The use of Xpert MTB/RIF improves case detection, shortens time to treatment, and results in more patients starting therapy earlier and reducing risk for transmission in the community (43). However, even when drug resistance is diagnosed, not all patients receive appropriate treatment. In 2013, 96,617 of the 136,412 patients with MDR TB whose cases were reported to WHO were enrolled in treatment, raising a serious ethical issue of expanding diagnostic services when treatment capacity cannot be matched (1). To date, only 29 out of 126 countries reporting outcomes for the 2011 cohort had reached the goal of successfully treating at least 75% of MDR TB cases (1). The treatment of drug-resistant cases is complicated by many challenges,
such as limited availability of second-line drugs, longer treatment duration, greatly increased costs, and high frequency of side effects (24). Of patients with MDR TB reported to WHO in the 2011 cohort, treatment success was 48% and 25% were lost to follow-up or had no outcome information (1). In certain advanced and severe cases, palliative care remains the only currently available option (44, 45).

HIV-ASSOCIATED TB

In 2013, HIV-associated TB constituted 25% of all TB deaths (among people living with and without HIV), and TB was the leading cause of death among people living with HIV worldwide (1). Of all HIV and TB incident cases, 78% were in sub-Saharan Africa, where 41% of TB cases were co-infected with HIV (1).

Recommended HIV and TB collaborative activities include strengthened case-finding and screening activities, use of primary services (including those dedicated to maternal and child health to detect and treat either the disease or the latent infection), provision of preventive therapy for people living with HIV, and an increase in infection control. For example, international recommendations promote isoniazid preventive therapy or other effective regimens and cotrimoxazole preventive therapy in addition to antiretroviral therapy for patients with TB and HIV (26). In contexts of high HIV prevalence, WHO recommends rapid molecular tests as the primary diagnostic tool for TB among people living with HIV (46). Although implementation of such interventions in some countries has increased, full coverage has not yet been reached in many settings.

ADDITIONAL CHALLENGES

Pediatric TB continues to be a poorly addressed problem (47), including a dearth of knowledge of drug resistance (48). Women will require additional attention, especially during their childbearing years (49, 50). Strengthened active case-finding activities, particularly among prioritized high-risk populations, will be required to further cut transmission through early detection and treatment.

Research and epidemiologic assessments have also revealed an association between TB and noncommunicable diseases (NCDs) and other conditions, such as diabetes mellitus, smoking, alcohol and substance abuse, malnutrition, and silicosis (51, 52). Cross-cutting efforts within and beyond the health sector in reducing such risk factors will aid in overall TB control.

The highlighted challenges call for responsive and well-functioning health systems to meet the evolving needs of future TB control. From 1990 to 2010, the proportion of aggregated global deaths attributed to communicable, maternal, neonatal, and nutritional causes decreased from 34.1% to 24.9%; the proportion of deaths caused by NCDs increased from 57.1% to 65.6% (53). However, as NCDs are prioritized, financial support for TB control must be ensured. This is especially relevant in settings without major external aid. In 2012, an additional $1 billion per year was needed for implementation, and $1.3 billion per year for research (23). Funding gaps have grown from $257 million in 2002 to $563 million in 2011; compared with 2011 levels, approximately $2 to $3 billion per year in additional funds are needed to reach the 2015 targets (32).

Continued investment in TB control should also be seen as part of comprehensive economic development agendas (54, 55). Low- and middle-income countries have the most to gain, with health improvements accounting for 24% of growth of full income between 2000 and 2011 (55). Tuberculosis control has long been highlighted as one of the most cost-effective public health interventions, and universal health coverage is now serving as a powerful means to bring TB deaths, as well as other preventable infections and maternal and child deaths, down to universally low levels (55).

Socioeconomic factors are ultimately the key determinants of poverty-related diseases, such as TB (56). As a social disease (57), TB thrives in the shadows of prosperity. Conditions associated with poverty (such as poorly ventilated and overcrowded housing) facilitate transmission, and malnutrition, alcoholism, and substance abuse promote its evolution into active disease. Moreover, the high prevalence of TB among underserved populations, such as the homeless, prisoners, minorities, migrants, and marginalized indigenous populations, within high-income countries is indicative of enduring inequities (51). Although control programs are essential to the care of persons affected by TB and to avoid deaths, improvements in socioeconomic conditions, reductions in income disparities, and political stability are crucial factors driving down the global epidemic (58–61).

CONCLUSION

Since 1990, important gains have been made toward reaching global TB targets set for 2015. Global action has included increased political commitment at the country level, strengthened international collaborations, and innovative partnerships among sectors at all levels toward better patient care. Although global incidence rates are slowly decreasing, the success of TB control varies greatly around the world, and major challenges pose serious threats to future control efforts. In particular, more than 3 million cases are missed by the health system, and the response to MDR TB is severely lagging behind established targets (1).

After 2015, TB control will confront extant and emergent challenges, including those directly related to the disease (such as drug resistance and co-infection with HIV) and broader issues (such as the increased prominence of NCDs and instability wrought by mounting income disparities). Sustained attention to TB control constitutes both a public health imperative and a vital component of economic development. Beyond 2015, global action should be based on strategies that exploit technical and operational innovations to improve TB control and promote universal health coverage and social protection mechanisms as a means to
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ensure access to quality care while avoiding catastrophic costs incurred by patients. Success will depend on rigorous implementation at the country and local levels and on the establishment of novel collaborations to tackle existing and emerging challenges.

From McGill University, Montreal, Quebec, Canada; University of Turin, Turin, Italy; and University of Padua, Padua, Italy.

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Requests for Single Reprints: Emilio Dirlikov, MA, Department of Anthropology, McGill University, 7th Floor, Leacock Building, 855 Sherbrooke Street West, Montreal, Quebec H3A-2T7 Canada; e-mail, emilio.dirlikov@mail.mcgill.ca.

Current author addresses and author contributions are available at www.annals.org.

References


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Current Author Addresses: Mr. Dirlikov: Department of Anthropology, McGill University, 7th Floor, Leacock Building, 855 Sherbrooke Street West, Montreal, Quebec H3A-2T7 Canada.
Dr. Raviglione: Global TB Programme, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland.
Dr. Scano: Disease Control, World Health Organization China Representative Office, 401 Dongwai Diplomatic Building, 23 Dongzhimenwai Dajie, Chaoyang District, Beijing 100600, PR China.

Author Contributions: Conception and design: E. Dirlikov, M. Raviglione, F. Scano.
Analysis and interpretation of the data: E. Dirlikov, M. Raviglione, F. Scano.
Drafting of the article: E. Dirlikov, F. Scano.
Critical revision of the article for important intellectual content: E. Dirlikov, M. Raviglione, F. Scano.
Final approval of the article: E. Dirlikov, M. Raviglione, F. Scano.
Administrative, technical, or logistic support: E. Dirlikov, M. Raviglione, F. Scano.
Collection and assembly of data: E. Dirlikov, M. Raviglione.

APPENDIX: SEARCH STRATEGY AND SELECTION CRITERIA
On 23 May 2013, a search for English-language articles was conducted on 2 electronic databases: PubMed and Science Direct. Articles were searched under the keywords “tuberculosis,” “global,” “control,” and policy,” published from 2007 to May 2013. The search returned 145 articles from PubMed and 68 from Science Direct. Articles were excluded if they focused on an individual country or region or exclusively on clinical research. A final 70 articles were reviewed. Additional background information was assembled from information provided by WHO headquarters and through discussions with TB experts. Two additional searches conducted on 5 January 2014 and 29 July 2014 identified 8 and 10 additional articles, respectively.