Ending tuberculosis by 2030: can we do it?

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SUMMARY

The Sustainable Development Goals aim to end tuberculosis (TB) related deaths, transmission and catastrophic costs by 2030. Multisectorial action to accelerate socio-economic development, a new vaccine and novel diagnostics and medicines for treatment are key advances needed to end TB transmission. Achieving 90-90-90 targets for TB (i.e., 90% of vulnerable populations screened, 90% diagnosed and started on treatment, and at least 90% cured) will help accelerate progress towards reductions in mortality; however, passive case detection strategies, multidrug-resistant TB, human immunodeficiency virus coinfection and outdated pathways to care need to be overcome. Ending the catastrophic costs associated with TB will require expansion of health insurance coverage, comprehensive coverage of TB services, and limited indirect costs by vulnerable and poor populations.

KEY WORDS: tuberculosis; Sustainable Development Goals; End TB Strategy

THE YEAR 2016 marks the beginning of the Sustainable Development Goal (SDG) era. By signing up to these goals, all countries have committed to ending the tuberculosis (TB) epidemic by 2030. Ending TB is defined by dramatic reductions in TB incidence and mortality, combined with zero TB-induced catastrophic costs for families (Figure 1).[1] This bold agenda deserves widespread support.[3] However, there are still difficult challenges. Here, we describe the major shifts needed to end TB.

ENDING TUBERCULOSIS TRANSMISSION

Among the Millennium Development Goals (MDGs) conceived in 2000, MDG 6 was aimed at halting and reversing TB incidence by 2015. This goal has been achieved. Since the year 2000, there has been an overall 18% reduction in the rate of TB incidence, with 9.6 million new cases estimated in 2014 (Figure 1).[2] In September 2015, the United Nations General Assembly adopted the SDGs, in which all countries agreed to reduce the 2015 TB incidence rate by 80% before 2030.[4]

The global SDG transmission target—<20 new cases per 100 000 population—was largely formulated based on reductions in incidence observed in high-income countries during their socio-economic development in the twentieth century.[5,6] Socio-economic conditions play a fundamental role in increasing TB risk.[7] Specifically, people with low socio-economic status are at increased risk of TB due to 1) increased exposure to TB because of crowded living and working conditions, 2) malnutrition, 3) limited knowledge about protective health behaviours, 4) use of solid fuels for basic energy needs, 5) limited access to health services, and 6) tobacco and/or alcohol abuse.[8] Many of these drivers of TB have the potential to be addressed within the next 15 years, as SDGs focus on poverty, hunger, education, clean energy and employment. For this reason, there will need to be close collaboration between different government ministries to harness the effects of socio-economic development on TB control. For example, in Southern Africa, where mining is an important risk factor for unskilled workers, health ministries could collaborate with 1) the ministries of labour, to provide high-quality protective equipment to reduce exposure to silica dust and improve ventilation to the extent possible in mining sites; 2) ministries of housing, to reduce crowding and improve ventilation in living quarters to reduce exposure to people with active disease; 3) ministries of social welfare, to ensure that minimum nutritional and sanitation requirements are fulfilled; and 4) ministries of industry, to ensure mining companies provide access to comprehensive health services.[9] It should be noted that while rapid levels of socio-economic development are theoretically possible for low- and middle-
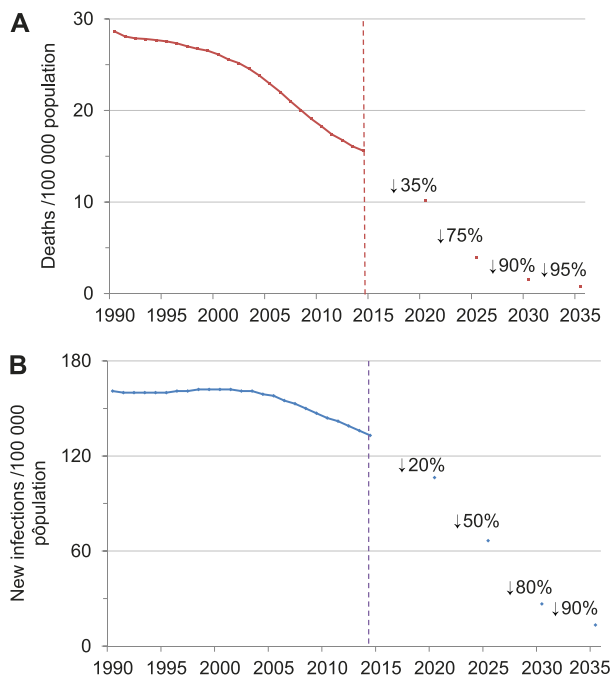
Figure 1 Global tuberculosis mortality **A)** and incidence **B)** trends and targets from 1990 to 2035.[3]

income countries (LMICs) during the SDG era, the TB community has to be prepared for setbacks in TB elimination caused by financial crises and new disease epidemics.[10,11]

Infection control remains the foundation for reducing TB exposure among non-infected individuals in health facilities and closed settings. These include administrative controls that minimise contamination of shared air by infectious subjects, environmental controls that minimise exposure to *Mycobacterium tuberculosis* through disinfection or removal of contaminated air, and personal protection measures that minimise inhalation of contaminated air.[12] Infection control has not, unfortunately, been prioritised in many LMIC settings. Accelerated implementation and enforcement by health authorities in both public and private health care settings is required to reduce all nosocomial infections, including TB. Within hospitals and other health care settings, the simplest ways to reduce transmission of *M. tuberculosis* are often the most effective; these include increasing the index of suspicion around patients with presumptive TB and separating them from others, investigating all presumptive TB patients rapidly for TB, separating patients with suspected multidrug-resistant TB (MDR-TB) from other TB patients, ensuring there are adequate windows that stay open and adding in skylights. Health care workers, especially those working on medical wards in high TB burden settings, are at high risk of TB; improved monitoring of TB in health care staff is urgently needed.[13] Studies from Latin America, Africa and Asia indicate that most TB transmission

occurs from unknown persons in the community.[14–16] Additional infection control measures in communities, such as changing the default requirements for ventilation in buildings and public transportation, and health education to increase the use of masks among people infected with respiratory diseases, merit research and exploration.

Vaccinating individuals is the most important health intervention to reduce their susceptibility to developing an infection. The bacille Calmette-Guérin (BCG) vaccine currently used in many LMICs has limited protective effects against TB.[17] Although some new prospects are in the pipeline, no vaccines have proved more effective than BCG to date.[18] Identifying a vaccine that is effective across age groups would help accelerate reductions in TB incidence to meet the SDG goals, and remains the key priority for the research community.[19] A major challenge to TB vaccine development is the lack of diversity in both the antigens included in the vaccines and the immune responses they elicit; research efforts are currently directed at broadening the antigen selection and the range of vaccine-mediated immune responses.[20] Previous and ongoing TB vaccine efficacy trials have enabled considerable research capacity to be developed. However, a larger investment is crucial if further trials of TB vaccine safety, immunogenicity and efficacy are to be realised. Moreover, potential risk factors for TB, such as diabetes mellitus (DM) and malnutrition, should be included and assessed in the study designs.

Although antiretroviral therapy (ART) is recognised as the most critical intervention for preventing human immunodeficiency virus (HIV) associated TB at the individual and population levels, it has not been recognised as a key intervention by many TB programmes.[21,22] The use of inexpensive, accurate, rapid and simple diagnostic tests for HIV, combined with safe, well-tolerated and effective ART, permits rapid scale-up of services through decentralised and task-sharing approaches.[23] New World Health Organization (WHO) guidelines recommending that ART be initiated among all persons living with HIV, irrespective of CD4 count, should facilitate global and national ART scale-up at a much earlier stage of immunosuppression than is currently the case.[24] In the high HIV-TB burden setting of southern Africa, achieving universal access to ART should be effective in reducing TB incidence.[25]

Implementing preventive treatment for latent tuberculous infection (LTBI) is necessary to reduce the number of people who develop active disease. However, this is hampered by technical problems, unresolved scientific uncertainties, and unclear service delivery approaches. Isoniazid (INH) preventive therapy (IPT) is currently recommended primarily for children aged <5 years in contact with patients who have infectious TB disease and for people living with
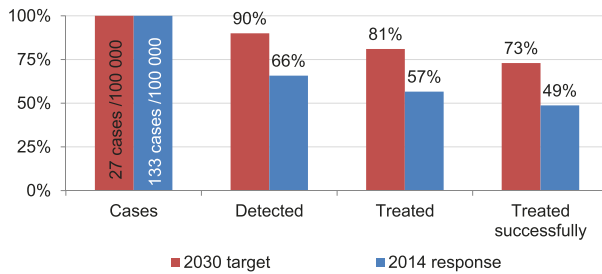
Figure 2   Current and target global tuberculosis cascades.[3]

HIV.[26,27] Given that the number of HIV-infected persons starting ART is likely to increase, IPT is expected to be administered more frequently with ART. Randomised controlled trials in South Africa and Cote d'Ivoire indicate a synergistic benefit of this approach, as IPT and ART together reduce the risk of TB by an additional 30% compared with ART alone.[28,29] Despite extensive scientific and programme experience, and the WHO endorsement of the efficacy and safety of IPT in children and people living with HIV, implementation of this intervention has been poor.[2] This is primarily due to technical issues with diagnosing LTBI and identifying the most appropriate treatment regimen.[30,31] INH remains the drug of choice, but the slight risk of drug-induced hepatitis causes both health care providers and asymptomatic persons to be reluctant about starting treatment, unlike with the generally non-toxic anti-retrovirals that are used to prevent transmission of infection in asymptomatic persons without HIV.[24] Less toxic and more acceptable preventive regimens could contribute significantly to TB elimination.

Increasing case detection and treatment success rates have reduced TB incidence in some settings.[32,33] Based on the simple principle that patients are non-infectious after cure, there is potential for rapid expansion of improved diagnostics and medicines to reduce population transmission of TB.[34,35] This requires improved linkages between diagnosis and treatment.[36] Importantly, studies indicate that the expansion of improved diagnostics and treatment in combination with other prevention interventions, such as an improved vaccine and programmatic management of HIV co-infection and MDR-TB, leads to the largest reduction in the burden of disease.[37]

ENDING TUBERCULOSIS DEATHS

Although TB mortality rates decreased by 47% between 1990 and 2014, there were an estimated 1.5 million TB deaths in 2014, 390 000 of which were associated with HIV infection (Figure 1).[2] The SDGs propose reducing 2015 TB mortality rates by 90%—to approximately two deaths per 100 000 population—before 2030.[4] The 90-90-90 targets for TB

control could enable this mortality target to be met.[38] Briefly, this target includes 1) 90% of vulnerable groups screened, 2) 90% diagnosed and started on treatment, and 3) at least 90% cured.[38] These targets, measured over a cascade, represent a different approach from the current monitoring, recording and reporting, where treatment success is assessed only for those registered for treatment rather than for those identified and diagnosed, a significant proportion of whom are never registered and never start treatment (Figure 2).[39] It will also require a change from the current information strategies which have, in many settings, insufficiently engaged the community or the private sector in the overall response to TB. Achieving the 90-90-90 targets will require screening strategies to be adapted to increase the number of persons diagnosed, while to increase cure rates, MDR-TB, HIV-co-infection, and current limitations in service delivery and health technology will need to be addressed.

While passive case finding, i.e., offering TB diagnostic services in health facilities, remains the foundation of TB diagnosis, it is insufficient on its own to screen 90% of vulnerable populations. Active screening of high-risk groups such as people living with HIV, incarcerated persons, miners and TB contacts, especially household child contacts aged under 5 years, can improve the number of people diagnosed and treated.[40–42] Screening other newly identified high-risk groups, such as persons with DM, may also merit programmatic implementation during the life course of the SDGs.[43] Unfortunately, there is little evidence to suggest that active case finding is widely embraced as a core programme strategy, and programmes must decide how to proceed with this approach. Innovative ways of addressing these issues in a sustainable manner, such as community-based multidisease screening and service delivery systems, need to be tested and implemented at scale.[44–46]

Pathways to care have changed little in the last 25 years, and for various reasons patients with infectious TB still often take months to be diagnosed.[47,48] There is an urgent need to develop and scale up simpler, cheaper and fully automated diagnostic systems based on nucleic-acid amplification technology that can be more readily implemented at point of care and diagnose TB patients earlier in the course of disease.[49] This may require the identification of novel biomarkers and more patient-friendly specimen collection sites.[49–51] For example, urine may be a suitable specimen in sick HIV-infected patients; a point-of-care urine-based lipoarabinomannan test used to guide the initiation of anti-tuberculosis treatment in sick HIV-positive hospital in-patients was found to significantly reduce 8-week mortality compared with routine diagnostic tests alone.[52] Treatment of patients with drug-susceptible TB is straightforward, and with good adherence should result in at least 90% of cases
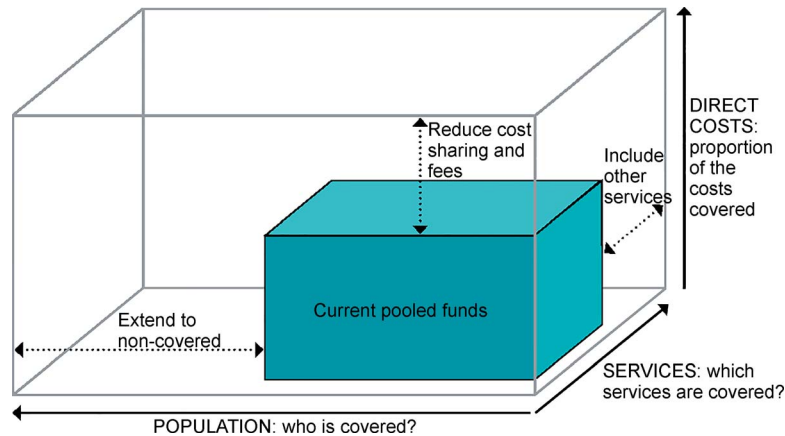
Figure 3   The three dimensions of universal health coverage.[5]

cured. However, the treatment course is still quite long and requires intensive monitoring by health facilities. Shorter, less toxic regimens could facilitate even higher treatment success rates while limiting financial externalities associated with missed work.[53]

MDR-TB, a disease caused by organisms resistant to both rifampicin (RMP) and INH, is a growing threat that compromises treatment outcomes. In 2014, MDR-TB accounted for 3.3% of new TB cases and 20% of previously treated TB cases worldwide, translating into approximately 480 000 cases per year.[2] Only 111 000 patients with MDR-TB (23%) started specific treatment, and the treatment success rate was 50%.[2] Sputum smear microscopy, the cornerstone of TB diagnosis for many years, cannot gauge bacterial susceptibility to TB. Some form of universal drug susceptibility testing—ideally at the time of the initial diagnostic test—should be embraced. The only diagnostic test that currently allows easy, rapid, sensitive and specific diagnosis, including information about RMP resistance, is the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA). This assay is now recommended by the WHO as the initial diagnostic test for all people requiring investigation for TB.[54] While significant strides have been made in scaling up and decentralising Xpert in various settings, operational issues still exist, and there is so far no evidence of impact on treatment outcomes or mortality.[55,56] More recently, the WHO has recommended second-line probe assays for detecting resistance to second-line anti-tuberculosis drugs.[57] The current expensive, toxic, 2-year treatment of MDR-TB is unacceptable and needs urgent change; shorter and less toxic regimens have shown promise and are now recommended by the WHO.[58–60]

The HIV epidemic has hampered TB control efforts globally. Over one million people develop HIV-associated TB annually, with three quarters of the burden coming from sub-Saharan Africa.[2] People with HIV and TB often have difficulty accessing care and treatment due to complex service delivery pathways. In 2014, only 51% of new TB cases had a documented HIV test result, and only 77% of those known to be HIV-infected were started on ART.[59] A broad range of collaborative activities have been proposed for coordinating prevention, service delivery and management of HIV-TB coinfection.[61] Unfortunately, many countries do not fully harness available tools to control the syndemic. For example, HIV and TB treatment remains accessible only in different health facilities in many countries, and for patients this implies a 'disconnect' between TB and HIV services.[62] Improved implementation of collaborative activities will be required to combat this syndemic.

ENDING CATASTROPHIC COSTS ASSOCIATED WITH TUBERCULOSIS

Universal health coverage (UHC), i.e., ensuring that all people obtain the health services they need without suffering financial hardship, has emerged as the health system foundation for health-related SDGs.[62] For the first time, global TB targets aim to reduce catastrophic costs associated with TB. Although the data were limited, a recent systematic review indicates that approximately a third of households with a TB patient experience TB-associated catastrophic costs.[63] Achieving zero TB-induced catastrophic costs for families will require TB programmes to reduce both the direct and the indirect costs of receiving TB services. UHC affects the direct cost of receiving TB services in three dimensions: populations covered, services covered and costs covered (Figure 3). Given that socio-economic determinants increase the risk of TB in poor and vulnerable populations, UHC schemes should ensure that these populations have both comprehensive coverage of TB diagnosis and treatment services as well as limited expenditure, as a means to improve UHC utilisation and TB outcomes. Schemes to reduce the indirect cost of receiving TB, such as transporta-

Table   Key actions required by TB stakeholders for eliminating TB

Civil society
- Increase awareness of adverse consequences of TB among vulnerable groups and poor populations
- Advocate for increased national investment into TB elimination through locally effective approaches

Donor community
- Invest in TB elimination from a long-term perspective and develop contingency plan for financial crises
- Diversify elimination financing to include non-state actors (e.g., companies, high net-worth individuals and philanthropic foundations)

Health workforce
- Improve accessibility of TB services (e.g., decentralise novel point-of-care diagnostics and engage non-governmental organisations for community-based service delivery approaches)
- Improve acceptability of TB services (e.g., create more services that respond to people's needs and expectations rather than TB disease itself)
- Improve affordability of TB services (e.g., reduce direct costs through universal health coverage and indirect costs through locally appropriate solutions)
- Implement comprehensive infection control measures in health facilities and explore feasibility of additional infection control measures in communities

International organisations and partnerships
- Ensure TB remains a global health and development priority
- Develop norms and standards for novel biomedical TB interventions
- Estimate resources and benefits associated with global TB elimination and mobilise resources to accomplish it

Scientific community
- Prioritise game-changers in TB elimination (i.e., a more effective vaccine, improved biomarkers for asymptomatic tuberculous infection, more effective medicines for treatment of MDR-TB, and point-of-care diagnostics)

TB = tuberculosis; MDR-TB = multidrug-resistant TB.

tion subsidies for poor and vulnerable populations, could further improve access to health services.[64] Nutritional support may also improve treatment uptake and completion rates among poor and vulnerable patients. Local pilot studies are needed to explore the feasibility of these interventions prior to national implementation. Increasing national economic growth and employment rates could also generate more financial resources for affected households to invest in health.

DISCUSSION

The goal to end the TB epidemic is an ambitious one that we fully support. TB services in high-income countries were initially scaled up because TB was a national scourge that for decades mobilised the full commitment of all layers of society, from primary school teachers to the top governmental ministries. This led to the construction and financing of well-functioning TB dispensaries, hospitals and sanatoria that offered free services for TB patients and their families. The implementation of the WHO's DOTS strategy in resource-limited settings was thought to be wildly over-ambitious and unrealistic by some. However, in reality, it inspired concerted international and national action, and led to the momentum that

ultimately resulted in universal access to TB diagnosis and treatment services.[65] The current ambitious TB goals for 2030 are just as important for inspiring, energising and persuading subnational, national and global communities to collaborate and step up the response to TB.

Nonetheless, achieving these goals will require major shifts in approach (Table). Diagnosis currently requires a laboratory infrastructure, which makes decentralisation, task sharing and national coverage difficult. The current treatment of MDR-TB is patient-unfriendly, and preventive treatment of LTBI is plagued by imperfect diagnostic technology and potentially toxic medicines. The new End TB Strategy crucially depends on new tools and interventions that may not be developed or scaled up in the next two decades. Monitoring and evaluation is based primarily on paper-based records, and the remarkable advances in information technology remain largely unharnessed.

Nearly US$12 billion per annum is needed to ensure a full response to the global TB epidemic.[2] An additional US$2 billion per annum is required to identify and advance novel TB vaccines, diagnostics and medicines.[2] There have been funding gaps and inefficiencies relative to the resources needed to end the TB epidemic, and in many settings this gap is growing due to competing health and development issues.[2] Community representatives, scientists and health care staff should convince their governments that TB elimination is a national cause and one to which their countries have signed up as part of the SDGs. Governments and international organisations could then ensure that TB elimination remains high on the development agenda. While the BRICS countries (Brazil, the Russian Federation, India, China and South Africa) that account for 50% of global TB cases mainly use domestic sources to fund TB control efforts, international donor funding, largely from the Global Fund and high-income countries, is needed for many other LMICs.[2]

Future national strategic plans should outline how TB elimination efforts, including sustainable and comprehensive insurance of high-quality TB services, are a national cause that is achieved in each endemic country. Monitoring implementation progress and effects on disease burden can help in sustaining this effort. In addition to ensuring adequate resources, there will also need to be a concerted effort to use funds far more efficiently and in a more focused manner. Engaging and empowering emerging stakeholders in the TB response—including private corporations and non-governmental organisations representing vulnerable populations—will also be needed to improve the response beyond routine health services. These stakeholders can help in a wide range of areas, such as garnering resource mobilisa-

tion, developing political commitment and delivery service.

CONCLUSION

Dynamic activism on the part of both TB programmes and civil society at large is crucial for the TB community to ensure that the global response is as robust and efficient as possible, using current technology, and asking for resources to develop new tools. Scientific research needs to focus on 'game changers', such as improved vaccines, biomarkers associated with asymptomatic tuberculous infection, improved point-of-care diagnostic tests and improved medicines for treatment. Multisectorial action could accelerate reductions in TB incidence through socio-economic development. Twenty years ago, the TB community demonstrated solidarity in developing and implementing the DOTS strategy. If we are to end the TB epidemic, this solidarity needs to be renewed, progress needs to be made in the areas we have outlined, and there must be willingness at all levels to do things differently.

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R E S U M E

Les Objectifs de Développement Durable visent à mettre fin aux décès liés à la tuberculose (TB), à sa transmission et aux coûts catastrophiques qu'elle engendre, d'ici 2030. Une action multisectorielle visant à accélérer le développement socioéconomique, un nouveau vaccin, de nouveaux tests diagnostiques et de nouveaux médicaments pour son traitement sont les progrès décisifs requis pour mettre fin à la transmission de la TB. Atteindre les cibles de 90-90-90 pour la TB (c'est-à-dire 90% des populations vulnérables dépistées, 90% des cas diagnostiqués et mis sous traitement et au moins 90% guéris) contribuera à accélérer les progrès vers une réduction de la mortalité. Il faut, cependant, dépasser les stratégies de détection passive des cas, vaincre la TB multirésistante et la co-infection au virus de l'immunodéficience humaine et adapter des parcours de soins obsolètes. Mettre fin aux coûts catastrophiques associés à la TB nécessitera une expansion de la couverture de l'assurance santé, une couverture spatiale complète des services liés à la TB et une limitation des coûts indirects supportés par les populations vulnérables et pauvres.

R E S U M E N

Los Objetivos de Desarrollo Sostenible tienen por finalidad poner término en el 2030 a las muertes, la transmisión y los costos catastróficos que genera la tuberculosis (TB). Las medidas multisectoriales encaminadas a acelerar el progreso socioeconómico y el desarrollo de nuevas vacunas, nuevos métodos diagnósticos y nuevos medicamentos constituyen avances primordiales, necesarios para interrumpir la transmisión de la enfermedad. El cumplimiento de las metas 90-90-90 en materia de TB (es decir, la detección sistemática del 90% de las poblaciones vulnerables, el diagnóstico y el inicio del tratamiento del 90% de los casos y una tasa de curación mínima del 90%) contribuirá a acelerar el progreso hacia una disminución de la mortalidad; sin embargo, todavía es necesario superar aspectos como las estrategias de detección pasiva de casos, la coinfección por el virus de la inmunodeficiencia humana y la TB y las trayectorias arcaicas de búsqueda de atención. Poner término a los costos catastróficos asociados con la TB exigirá una ampliación de la cobertura del seguro de enfermedad, una cobertura exhaustiva de los servicios de TB y la disminución de los costos indirectos que pesan sobre las poblaciones vulnerables y pobres.