Global Fund TB Landscape Analysis, 2016-2020

2. Tuberculosis

2.a Executive Summary

2.1 The 2015 MDG of halting and reversing TB incidence has been achieved globally and incidence has been declining at 1.5% per year on average since 2000. However, about 3 million incident cases per year are not reported and 1.5 million die each year in spite of TB being a preventable and curable disease.

2.2 The WHO End TB Strategy aims to accelerate the present slow decline in TB burden, with the goals of ending the global TB epidemic by 2035, and 2025 milestones of a 75% reduction in TB deaths and a 50% reduction in the TB incidence rate. No tuberculosis-affected person or family should face catastrophic costs due to tuberculosis care after 2020.

2.3. To achieve universal access to TB services, and reduce TB incidence faster, more investment is essential. In 2015, the budget gap is estimated at about US$ 2 billion. BRICS countries in particular are already mobilizing considerable domestic resources, and could do more. International donor funding should focus on countries with high burdens relative to their resources, including some middle-income countries with high burdens of multidrug-resistant TB (MDR-TB).

2.b. Estimated Disease Burden

2.4 In 2013, an estimated 9 million people developed TB and 1.5 million died from this preventable and curable disease[1]. TB incidence has been slowly declining since 2004, in part because diagnosis and treatment are increasingly available. In 2013, nearly two-thirds of the 9 million cases were diagnosed, notified to WHO, and started on treatment. TB diagnosis and treatment saved about 37 million lives between 2000 and 2013. The 2015 MDG of halting and reversing TB incidence has been achieved globally, and in all six WHO Regions.

2.5 An estimated 1.1 million (13%) of the 9 million cases diagnosed with TB in 2013 were among people living with HIV (PLHIV) and 360,000 deaths occurred among HIV-positive TB cases, accounting for 25% of all TB deaths[2]. Worldwide, about 3.5% of all new cases, and 20.5% of previously treated cases have MDR-TB. On average, an estimated 9% of people with MDR-TB have extensively drug resistant TB (XDR-TB). In 2013, an estimated 480,000 incident cases of MDR occurred and 210,000 people died from MDR-TB. There were an estimated 300,000 cases of MDR-TB among the TB cases who were notified in 2013; of these, 136,000 were diagnosed as MDR-TB, up from 50,000 cases in 2010. Only 97,000 (20% of the estimated total), however, received treatment for MDR-TB in 2013.

2.6 More than half of those developing TB in 2013 did so in the South-East Asia and Western Pacific Regions (of WHO). India and China alone accounted for 23% and 11% of total cases, respectively. A further quarter of cases were from the African Region, which had the highest rates of cases and deaths relative to the population. This was because four of every five HIV-affected TB patients and TB deaths in HIV positive people occurred in that Region. HIV co-

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1 WHO. Global Tuberculosis Report, 2014. WHO, Geneva.

2 Ibid.

infection ranged from 7% in Mali to 74% in Lesotho and Swaziland. Over 60% of global MDR-TB cases occurred in India, China and Russia, and the highest MDR-TB rates have consistently occurred over the past 20 years in countries of the former Soviet Union. The high levels of drug resistance account for the low treatment success rate (75%) among new cases in 2013 in the European Region, the lowest of all six regions.

Figure 1. **a) Graph of incidence and countries – Top 10, next 12 and others**

b) Estimated TB incidence rates, 2013

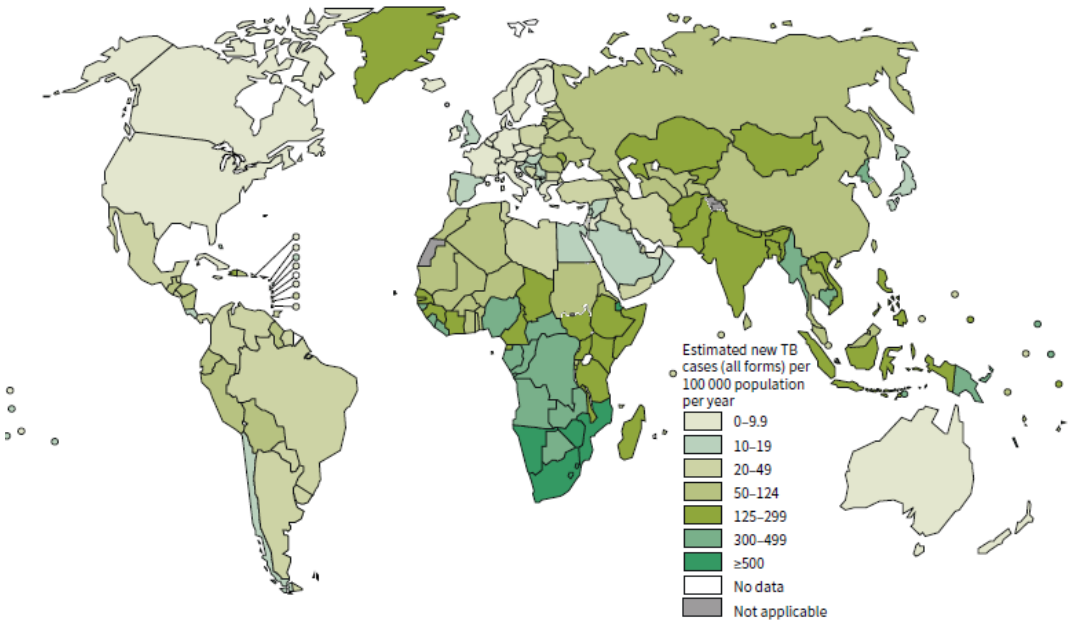
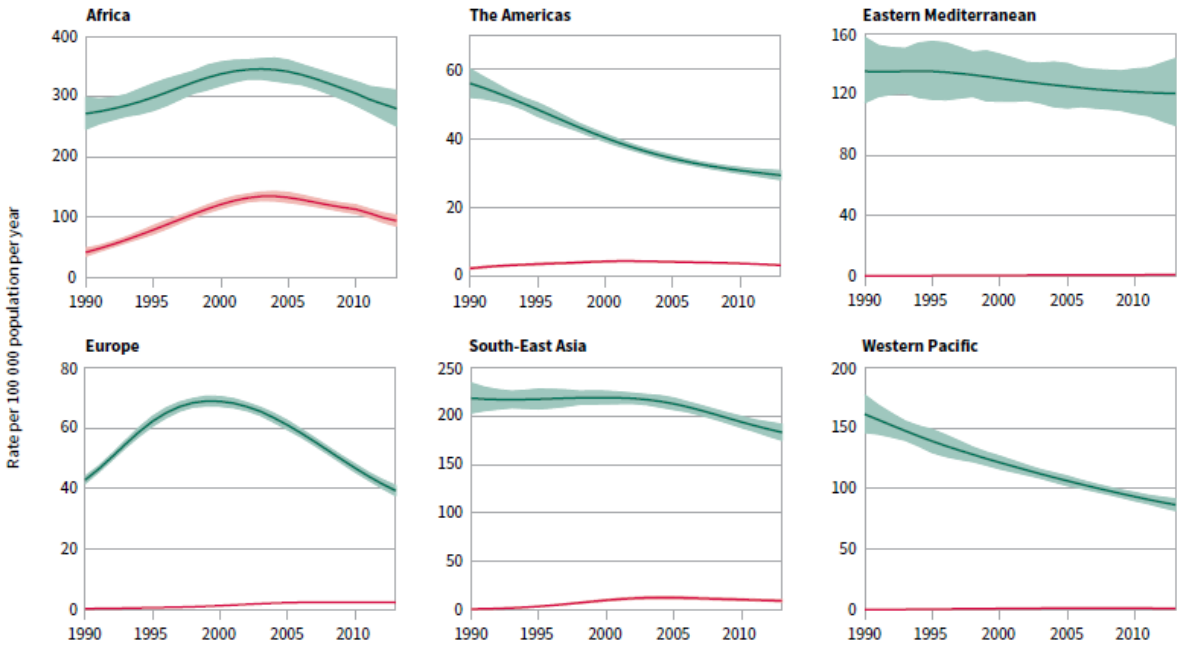


Figure 2. Estimated TB incidence rates by region, 1990-2013. Regional trends in estimated TB incidence rates (green) and estimated incidence rates of HIV-positive TB (red). Shaded areas represent uncertainty bands.



2.c Unmet Needs

2.7 Overall, 3.3 million TB cases in 2013 either did not get a diagnosis, or did so, but were not reported to national TB programmes. Children are still underdiagnosed relative to their estimated TB burden. Recent national TB prevalence surveys have shown greater burdens in some African countries than previously thought, and also higher than previously estimated burdens in Indonesia and Laos (in other countries, survey results were consistent with previous estimates). As a result, estimates of the global burden (cases and deaths) of TB in 2015 will be higher than those published in 2014.

2.8 Globally, in 2013, more than half (52%) of notified TB cases were not tested for HIV. The number of HIV infected people with TB started on anti-retroviral treatment (ART) was only 32% the estimated HIV positive TB patients in 2013. Only 21% of countries report provision of isoniazid preventive therapy (IPT) to PLHIV. Over 300,000 MDR-TB cases did not get a diagnosis in 2013, and of the 136 000 cases diagnosed and reported in 2013, 39,000 (29%) were not treated. Services required for MDR-TB management including biochemistry testing, audiometry and ECGs with automatic measurement of QT intervals, are generally lacking. Infection control fails to make use of existing technologies such as surgical masks and respirators. Globally, only 48% of those treated for MDR-TB had a successful outcome.

2.9 Underlying reasons for these unmet needs are frail health systems that are underfunded, understaffed, with poorly qualified workers, poor infrastructure and under-the-table payments. All this points to a persistent need to make health services, and especially diagnostic services, more accessible and accountable, and health workers more able to diagnose, treat and report TB cases. In order to find TB patients earlier in the course of their illness, a wider range of stakeholders already involved in community-based activities needs to be engaged. These include the nongovernmental organizations (NGOs) and other civil society organizations (CSOs) that are active in community-based development, particularly in primary health care, HIV services and maternal and child health, but have not yet included TB in their priorities and activities. A significant part of the "missing" cases is due to patients attending the private sector (particularly in India and Indonesia) where the quality of diagnosis and treatment is uncertain, costs for patients are high, and failure to report to the TB Programme is common. A radical new approach towards the private sector is needed.

2.10 Treatment success has improved over the past decade, and overall was 86% in 2013[3]. However, only 76% of TB cases among PLHIV reported in 2012 were successfully treated compared to 88% of HIV-negative cases. Overall, in the MDR-TB cohort starting treatment in 2011, only 48% were successfully treated[4], although data are incomplete. Programmes need a better understanding of the reasons for poor outcomes, and they should be more stringent in their application of international standards for the programmatic management of DR-TB. The approximately 10-20 fold difference in the cost of treating a drug resistant case compared with a drug sensitive one means that fiscal disaster threatens many programmes unless they can prevent MDR-TB from occurring in the first place.

2.11 In most countries, poor outcomes are concentrated in key affected populations (KAP), such as children, prisoners, migrants, refugees, slum dwellers, the homeless, nomadic populations, miners, the immunosuppressed, and the elderly. While access to services for some

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3 Ibid.

4 Ibid.

of these groups has improved since 2010, much remains to be done. Within countries, there are significant geographical variations in TB burden and outcomes, which are often not addressed.

2.d Key Advances

Type	Existing	Anticipated	Timing	Likelihood	Impact
Vaccine	BCG	Mtb72F+ASO1E	2020	V low	Potentially very high
Treatments Drug sensitive	Rifampicin/ Isoniazid/ Pyrazinamide/ Ethambutol.	For both sensitive and MDR strains: pretomanid, moxifloxacin+ pyrazinamide.	2018	Medium/high	High
MDR-TB	Laevofloxacin or moxifloxacin + amikacin or kanamycin or capreomycin + ethionamide or prothionamide + cycloserine and/or PAS + bedaquiline or delamanid.	Pretomanid, linezolid and bedaquiline.	2020	Medium	High
XDR-TB	Linezolid + imipenem/cilastatin + clofazimine + any of above to which strain is sensitive.	Regimens containing bedaquiline and delamanid	2017	High	Medium
Diagnostics[5]	Sputum smear Culture (solid/liquid) Molecular tests	Xpert MTB/RIF Ultra, Xpert MTB/RIF XDR, Alere qTB, Alere qDST, Truenat, Easynat.	2016 2017 2018	High	Medium Medium/high
		Digital X-ray with automated computer aided reading	2016	High	Medium/high
TB/HIV	ART/3Is	Isoniazid + rifapentine once weekly regimen for 12 weeks	2018	High	Medium

In general, there is a need to roll out new tools and use them in the field much faster than previously.

[5] Stop TB Partnership. Bending the Curve: a global investment framework to win the fight against TB. 2015. In draft.

Vaccine

2.12 The lack of efficacy of the recent MVA85A trial in infants illustrates that neither known correlates of vaccine immunogenicity nor existing animal models proved predictive of vaccine efficacy[6]. Choosing what candidates go into prohibitively expensive trials thus remains a guessing game. Advances that will positively affect practice are not expected before the end of 2020. BCG will remain in use as a vaccine that prevents the disseminated forms of TB that used to occur in childhood.

Treatments

2.13 Against expectation, recent trials of fluoroquinolones have not allowed any reduction in drug susceptible treatment duration[7,8]. However, for the first time in over 50 years, two new drugs specifically developed for TB, bedaquiline and delamanid, have been introduced for the management of MDR-TB only, with encouraging results[9,10]. Studies, some including bedaquiline, may enable the reduction of treatment duration of MDR-TB in the next five years. The results of studies on a regimen made up of Pa 824, moxifloxacin and pyrazinamide, that may prove effective against currently drug resistant as well as drug sensitive strains, are expected around 2018[11]. Disruptive advances in the treatment of TB are therefore likely before 2020.

Diagnostics

2.14 It is in diagnostics that new tools have had the biggest impact. In diagnosis, phenotypic tests are giving way to molecular ones (in follow up tests, however, the phenotypic ones remain the standard). Successful introduction of the Xpert MTB/Rif test has made the diagnosis of TB more accurate (that is, more sensitive and more specific, than sputum smear microscopy). In addition, line-probe assays (LPA) and Xpert MTB/Rif have greatly reduced the time taken for diagnosis of MDR-TB[12] but it has also shown that health systems need significant upgrading to make best use of such beneficial but disruptive technologies[13]. New diagnostic algorithms need

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6 Ibid.

7 Merle CS, Fielding K, Sow OB et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. N Engl J Med. 2014 Oct 23;371(17):1588-98. doi: 10.1056/NEJMoa1315817.

8 Gillespie SH, Crook AM, McHugh TD et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. N Engl J Med. 2014 Oct 23;371(17):1577-87. doi: 10.1056/NEJMoa1407426. Epub 2014 Sep 7.

9 Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med. 2014 Aug 21;371(8):723-32. doi: 10.1056/NEJMoa1313865.

10 Gler MT, Skripconoka V, Sanchez-Garavito E, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med. 2012 Jun 7;366(23):2151-60. doi: 10.1056/NEJMoa1112433.

11 Dawson R, Diacon AH, Everitt D et al. Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis. Lancet. 2015 May 2;385(9979):1738-47. doi: 10.1016/S0140-6736(14)62002-X. Epub 2015 Mar 18.

12 Drobniewski F, Cooke M, Jordan J, et al. Systematic review, meta-analysis and economic modelling of molecular diagnostic tests for antibiotic resistance in tuberculosis. Health Technol Assess. 2015 May;19(34):1-188. doi: 10.3310/hta19340.

13 WHO. Xpert MTB/RIF implementation manual. Technical and operational 'how-to': practical considerationshttp://www.who.int/tb/publications/xpert_implem_manual/en

to be worked out, and new communication systems need to be put into place to ensure that the advantages of a rapid diagnosis can be translated into a faster clinical response[14]. All populations need equitable access to the new technologies. The high cost of Xpert machines and cartridges are an inhibitory factor, but further developments of the Xpert platform are anticipated in the next five years, and competitor products may also arrive in the field, perhaps enabling a point of care test[5].

2.15 The cost of the Xpert platform has driven the development of chest radiology as a lower cost screening test in some countries' diagnostic algorithms. Digital radiology techniques, with computer-aided diagnosis, are likely to make an impact before 2020.

HIV/TB

2.16 The challenge is to expand existing interventions such as antiretroviral therapy (which is already reducing TB occurring in PLHIV) and the three I's: isoniazid preventive therapy (IPT), intensified TB case-finding among people with HIV, and infection control to prevent the spread of TB in health facilities. The reduced duration three-month course of INH and rifapentine (3HP)[15] is a promising advance for expanding preventive therapy. Ultra violet germicidal irradiation (UVGI) lamps[16] also hold promise for infection control in clinics and congregational settings.

Demand implications

2.17 A new vaccine will not be available during 2016-2020, but new molecular diagnostic tests are likely to be approved by WHO for use in the field. Greater access to better testing will likely double the number of MDR-TB cases diagnosed annually by 2020, which will require more second-line treatment at significantly greater expense. New drugs with shorter regimens will likely enter service as treatment for drug-resistant cases. The new drugs will be expensive, but treatment durations will probably be shorter. New information, communications technology (ICT) systems will drive improvements in many areas, such as diagnostic results, verification of treatment, e-learning and surveillance.

2.e Partner Landscape and Funding Environment

2.18 An estimated US$xx billion per year is required for 2016-2020 to ensure a full response to the global TB epidemic, of which XXXX is for TB specific care and XXXX is for health system costs. In 2014, funding for TB prevention, diagnosis and management reached US$ 6.3 billion in 122 countries that make up 95% of reported cases[1]. A further US$2 billion is required for research and development for new TB tools[1].

2.19 Above 85% of the reported funding in 2014 was from national domestic resources – including almost 2 billion from Russia. The BRICS countries, Brazil, the Russian Federation, India, China and South Africa, collectively account for 50% of global cases and could find the whole, or a very large part, of the required funding within their own resources. International

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[14] The role of e/mHealth in tuberculosis and tobacco control : a WHO/ERS consultation. Meeting Report. (WHO/HTM/TB/2015.12) [Internet]. Geneva, World Health Organization; 2015 May. Available from: http://www.who.int/tb/features_archive/emHealthinTBandtobaccocontrol.pdf

[15] Sterling TR, Villarino ME, Borisov AS et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011 Dec 8;365(23):2155-66. doi: 10.1056/NEJMoa1104875.

[16] Mphahlele M[1], Dharmadhikari AS, Jensen PA et al. Institutional Tuberculosis Transmission: Controlled Trial of Upper Room Ultraviolet Air Disinfection - A Basis for New Dosing Guidelines. Am J Respir Crit Care Med. 2015 Apr 30. [Epub ahead of print]

donor support, however, is essential for many other countries, including the 17 non-BRICS, high burden countries, where it accounted for more than 50% of total funding in 2014. In most low-income countries, more than 90% of the available funding in 2014 was from international donor sources[1].

2.20 In 2014, the Global Fund was the largest international donor for TB, followed by the US Government, particularly USAID. Other key partners in TB include international organizations such as the WHO, the World Bank, Stop TB, UNAIDS, and bilaterals such as DFID (UK), the Cooperation Francaise and the Japan International Cooperation Agency. Many NGOs are involved, such as the Union (against TB and Lung Disease), Médecins Sans Frontières, KNCV, and the Red Cross.

2.21 The End TB Strategy, approved by the World Health Assembly in 2014, has as its goals the ending of the global TB epidemic by 2035, and 2025 milestones of a 75% reduction in TB deaths and a 50% reduction in the TB incidence rate. No tuberculosis-affected person or family should face catastrophic costs due to tuberculosis care after 2020. Full funding of this strategy will require international donor funding of US$ XXXX billion/year.

2.f Key Issues and Implications for the Global Fund

Issue	Implication for the Global Fund
The global targets of the WHO End TB Strategy, consistent with the Global Plan of the Stop TB Partnership, are shifting the direction from "controlling TB" to "ending TB"	This shift, and reaching the End TB targets, will require increased funding.
From 2015, the TB burden will be higher than previously estimated, as a result of recent prevalence surveys	• Current levels of coverage and access to TB services – especially for those most affected and vulnerable – need to be raised. Innovative approaches to increase case finding, access to services and effective treatment are required. • Interventions aimed at strengthening national health information systems to get accurate measurements of the burden and to plan for differentiated responses are needed. • Addressing these issues will increase costs.
70% of the TB burden is in Middle Income countries, including BRICS	• A larger focus on leveraging domestic resources, including policy shaping and advocacy, and supporting countries to develop plans based on domestic funding of TB programmes • Working with TB partners to ensure that there is a coordinated approach in addressing TB within BRICS, including South-South support and financial support to global efforts
Achieving the WHO END TB targets will require greater access to health services (diagnostic and treatment services), including greater penetration in private health system and for key populations	• Investments in health and community systems and the promotion of integration and synergies between the 3 diseases should continue • Strategic investments in private health systems will be needed to promote behaviour change towards support of public health programmes such as ending TB • Interventions that increase access to care for key populations and vulnerable groups, will need increased support, addressing barriers related to gender, human rights and discrimination
New diagnostic tests, new drugs, regimens and combinations, are likely to be approved for use in the field for both drug-sensitive and resistant TB and for prevention among PLHIV.	Increase in demand for Global Fund support to introduce new tools including policy revision, staff training and retaining, infrastructure support, introduction of quality management systems, pharmacovigilance, equipment validation, maintenance systems and joint TB and HIV programming.
The END TB strategy calls for universal health coverage, including Universal DST	There are significant budgetary implications to all TB patients having a DST result at the start of treatment. A huge need for resources for treatment of drug resistant TB needs to be balanced with increased efforts to prevent drug resistance.
ICT is underexploited in TB care and prevention although it is expanding in low and middle-income countries and could contribute in many areas to reaching End TB Strategy goals by making better use of currently available tools	Greater investment in ICT to improve patient care (eg verification of treatment by video for MDR patients), surveillance (eg improving notification), laboratory information management and e-learning.