Rethinking Global Pharmaceutical Policy

William Fisher and Talha Syed

Appendix 1: Tuberculosis

(version 1, December 2024)

Tuberculosis (TB) has been with us for millennia. The bacteria that causes the disease appears to have developed in East Africa at least 15,000 years ago and to have accompanied human populations as they dispersed throughout the globe. Evidence of the disease has been found among the remains of most major civilizations, including those of ancient Egypt, classical Greece, and ancient Chile. Descriptions of it appear in the Old Testament and venerable texts from India and China.[1] During the nineteenth century, roughly one quarter of all deaths in Europe resulted from TB.[2]

Today, the overwhelming majority of TB cases result from one species of bacteria, *mycobacterium tuberculosis*, but a few cases result from other members of the same family: *mycobacterium bovis* (which was a more serious threat to humans prior to the widespread pasteurization of milk); *mycobacterium africanum* (which causes a substantial minority of the cases in West Africa);[3] *mycobacterium caneti* (confined to the Horn of Africa); and *mycobacterium microti* (which sometimes occurs in HIV-positive persons).

The primary way in which the TB bacteria are transmitted is through the inhalation of water droplets suspended in air that has been contaminated by a cough or sneeze from someone with an active TB infection.[4] A few of those droplets reach the alveoli in the recipient's lungs, where the bacilli multiply; eventually, they spread to the lymph nodes and onward to other organs in the body.[5] An immune response usually kills off most of the bacilli, leaving behind granulomas (clusters of immune cells) in the tissue.[6] At this point, the person is said to be "infected," but is asymptomatic.

The large majority of TB infections remain latent indefinitely. However, either because the initial infection overcomes the host's immune system or because a secondary infection reactivates latent bacilli, some patients develop the disease commonly referred to as "tuberculosis."[7] Typically the disease causes most damage to the lungs, but it can injure almost

---

[1] See Thomas M. Daniel, "The History of Tuberculosis," *Respiratory Medicine* 100 (2006); Salmaan Keshavjee and Paul E. Farmer, "Tuberculosis, Drug Resistance, and the History of Modern Medicine," *New England Journal of Medicine* 367 (2012).

[2] See Barry R. Bloom, ed., Tuberculosis: Pathogenesis, Protection and Control (1994).*

[3] See Bouke C. de Jong et al., "Diferences between Tuberculosis Cases Infected with Mycobacterium Africanum, West African Type 2, Relative to Euro-American Mycobacterium Tuberculosis: An Update," *FEMS Immunology & Medical Microbiology* 58 (2010).

[4] *See* Core Curriculum on Tuberculosis: What the Clinician Should Know, 4th Edition (2000) Division of Tuberculosis Elimination Centers for Disease Control and Prevention (CDC) (Internet Version updated Aug 2003), at 5. Patients with latent infection are not generally capable of transmission. *See id.*

[5] *See id.* at 7.

[6] See id.

[7] See id.

any part of the body. Its principal internal manifestations are small white tubercles in tissues, scarring of the lobes of the lungs, and abnormal lung cavities. Common symptoms include chronic cough, fever, chills, night sweats, fatigue, and weight loss. If untreated, the disease leads to death within a decade more often than not.[8]

Today, the main treatment for active TB is a course of antibiotics.[9] The drugs most commonly used are rifampicin and isoniazid. They are now often combined with two more: ethambutol and pyrazinamide.[10] Unfortunately, TB bacteria are unusually hardy. As a result, an effective cure typically requires a sustained course of drugs – at least 6 months. Partly because of the duration of treatment and partly because the drugs have unpleasant side effects, some patients fail to complete the course conscientiously.[11] Their lapses accelerate the development of drug-resistant strains of the bacteria in their bodies, which not only reduces their own responsiveness to antibiotics, but heightens the hazard that they pose to others. The "Directly Observed Therapy Short-course" (DOTS) (developed by the WHO[12]), in which a health-care worker monitors each patient's consumption of the antibiotics,[13] is intended (among other things) to minimize such lapses, but its effectiveness in this particular respect is doubtful.[14]

Several varieties of drug-resistant resistant strains have now been identified.[15] "Rifampicin-resistant TB" (RR-TB), as its name suggests, is unaffected by one of the two most common first-line antibiotics. In 78% of the cases involving RR-TB, the strain is also resistant to isoniazid – and is thus classified as "Multiple-drug-resistant TB" (MDR-TB). Infections caused by these two strains are usually curable – but only with a painful two-year regimen of toxic drugs that can have severe side effects.[16] "Extensively-drug-resistant TB" (XDR-TB) is worse still; it is unaffected by a majority of the second-line drugs. Last but not least, "totally-drug-resistant TB" (TDR-TB) is unaffected by all known antibiotics.[17] Roughly 3.4% of all new cases of active TB

---

[8] See Tiermerma EW, "Natural History of Tuberculosis: Duration and Fatality of Untreated Pulmonary Tuberculosis in Hiv-Negative Patients: A Systematic Review," *PLoS ONE* 6, no. 4 (2011).

[9] For the set of antibiotics that the WHO deems "essential" in treating TB, see WHO, "Model List of Essential Medicines," (2013), 9-10.

[10] See "Global Tuberculosis Report," (2014), 1. More details concerning the courses of antibiotics recommended by the WHO may be found at *Treatment of Tuberculosis Guidelines*, 4th ed. (Geneva2009), 29-51.

[11] *See* Stefan H.E. Kaufman & Hans-Willi Mittrucker, *Vaccination against Tuberculosis: Current Status and Future Promise*, SEMINARS IN RESPIRATORY AND CRITICAL CARE MEDICINE Vol. 25, No. 3 at 346 (2004).

[12] See WHO, "The Stop Tb Strategy: Building on and Enhancing Dots to Meet the Tb-Related Millennium Develpment Goals," (2006).

[13] See "Implementing the Stop Tb Strategy: A Handbook for National Tuberculosis Control Programmes," (2008), 32.

[14] See Jimmy Volmink and Paul Garner, "Directly Observed Therapy for Treating Tuberculosis," *Cochrane Database of Systematic Reviews*, no. 4 (2007), http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003343.pub3/abstract;jsessionid=E1CD2AD70A259A19D3DF7F9FB38DC901.f01t02.

[15] See WHO, "Drug-Resistant Tb: Surveillance and Response," (2014).

[16] See Patrick Adams, "Losing the Fight against Tuberculosis," *New York Times*, January 5, 2015 2015.

[17] MDR-TB and XDR-TB are now well-recognized clinical categories. Whether the term TDR-TB is useful is subject to some debate. Compare Velayati et al., "The Totally Disease Resistant Tuberculosis," Int J Clin Exp Med. 2013; 6(4): 307–309, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3631557/, with Keertan Dheda et al., "Global Control of Tuberculosis: From Extensively Drug-Resistant to Untreatable Tuberculosis," *Lancet Respiratory Medicine* 2 (2014). Some observers argue for recognition of a fifth category (between XDR-TB and TDR-TB), known as "extremely drug-resistant TB") (XXDR-TB). See G.B. Migliori et al., "Totally Drug-Resistant and Extremely

now take one of these drug-resistant forms. The most dangerous variant, TDR-TB, has been documented in Italy, India, Iran, and South Africa.[18]

Another alarming development is the synergy of TB and HIV. An HIV infection, by degrading the person's immune system, sharply increases the likelihood that a TB infection that the person already has or later acquires will become active. To reduce this probability, HIV-positive persons can and should be given prophylactic doses of isoniazid.

A vaccine for TB does exist. Commonly known as BCG (after its developers, Albert Calmette and Camille Guérin), it is based on a strain of *Mycobacterium bovis* that was attenuated a century ago.[19] It is currently administered to approximately 100 million persons a year.[20] BCG has proven to be highly effective in preventing TB infection during childhood.[21] Unfortunately, it is much less effective in preventing pulmonary TB in adults.[22] A number of hypotheses have been suggested to explain this phenomenon. Some scientists contend that the protection induced by BCG wanes over time.[23] Others believe that variation in the strains of the TB bacteria accounts for the differences in protection afforded by the vaccine.[24] The most popular explanation, however, is that an individual's active immune response to non-pathogenic organisms may inhibit the *in vivo* replication of the BCG vaccine required for its protective effect.[25] Whatever the reason, BCG provides adults little protection against the disease.

Today, between one quarter and one third of the world's population is infected with one of the tuberculosis strains. [26] Over 10 million people develop the active form of the disease each

---

Drug-Resistant Tuberculosis: The Same Disease?," 54 Clinical Infectious Diseases 1379 (2012), available at http://cid.oxfordjournals.org/content/54/9/1379.full.pdf.

[18] See Katherine Rowland, "Totally Drug-Resistant TB Emerges in India," Nature, January 13, 2012, http://www.nature.com/news/totally-drug-resistant-tb-emerges-in-india-1.9797.

[19] See Helen McShane et al., Boosting BCG with MVA85A: the first candidate subunit vaccine for tuberculosis in clinical trials, TUBERCULOSIS Vol. 85 at 47 (2005).

[20] *See* Stefan H.E. Kaufman & Hans-Willi Mittrucker, *Vaccination against Tuberculosis: Current Status and Future Promise*, SEMINARS IN RESPIRATORY AND CRITICAL CARE MEDICINE Vol. 25, No. 3 at 346 (2004).

[21] See A Roy and et al., "Effect of Bcg Vaccination against Mycobacterium Tuberculosis Infection in Children: Systematic Review and Meta-Analysis," *British Medical Journal* 349 (2014).

[22] *See supra* Brennan at 7.

[23] *See supra* Doherty at 818.

[24] *See supra* Brennan at 10. Alternatively, the differences may be caused by methodological differences in dosage and delivery. *See id.*

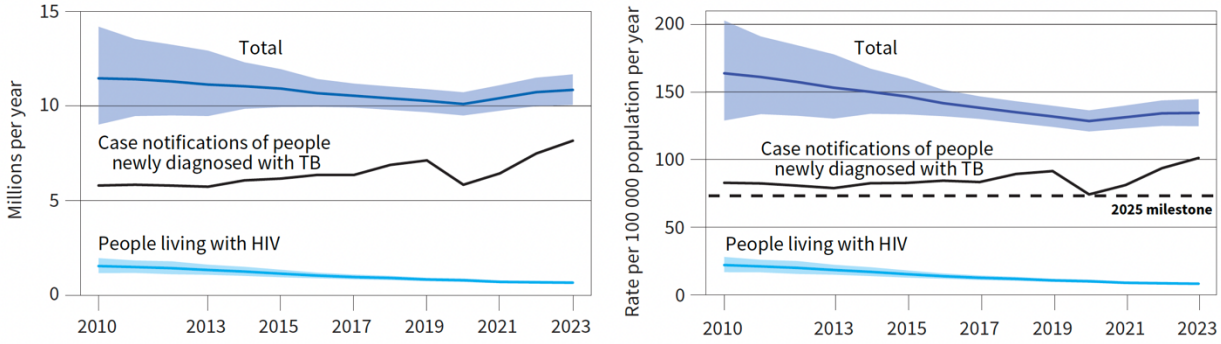
[25] *See* S.G. Reed et al., *Prospects for a better vaccine against tuberculosis*, TUBERCULOSIS, Vol. 83 at 214 (2003). This explanation has been labeled the Koch phenomenon and is based on the idea that the antigens being regulated by the immune response actually trigger the "necrosis of pre-existing tubercle foci, release of organisms previously walled-off within this granuloma, spread of infection and increasing pulmonary destruction." *Id.*

[26] See Zhou Xing, Mangalakumari Jeyanathan, and Fiona Smaill, "New Approaches to Tb Vaccination," *CHEST* 146, no. 3 (2014).

year.[27] Both the raw number and the incidence rate have been rising since 2021. The following figures, provided by the WHO, show the recent history.[28]

Global trends in the estimated number of incident TB cases (left) and the incidence rate (right), 2010–2023

The horizontal dashed line shows the 2025 milestone of the End TB strategy, which is a 50% reduction in the TB incidence rate between 2015 and 2025. Shaded areas represent 95% uncertainty intervals.



Many of the new active cases are of HIV-positive people, and 250,000 of the deaths result from the interaction of TB and HIV.[29] The following figure, also provided by the WHO, show the geographic distribution, as of 2023, of new TB infections.[30]

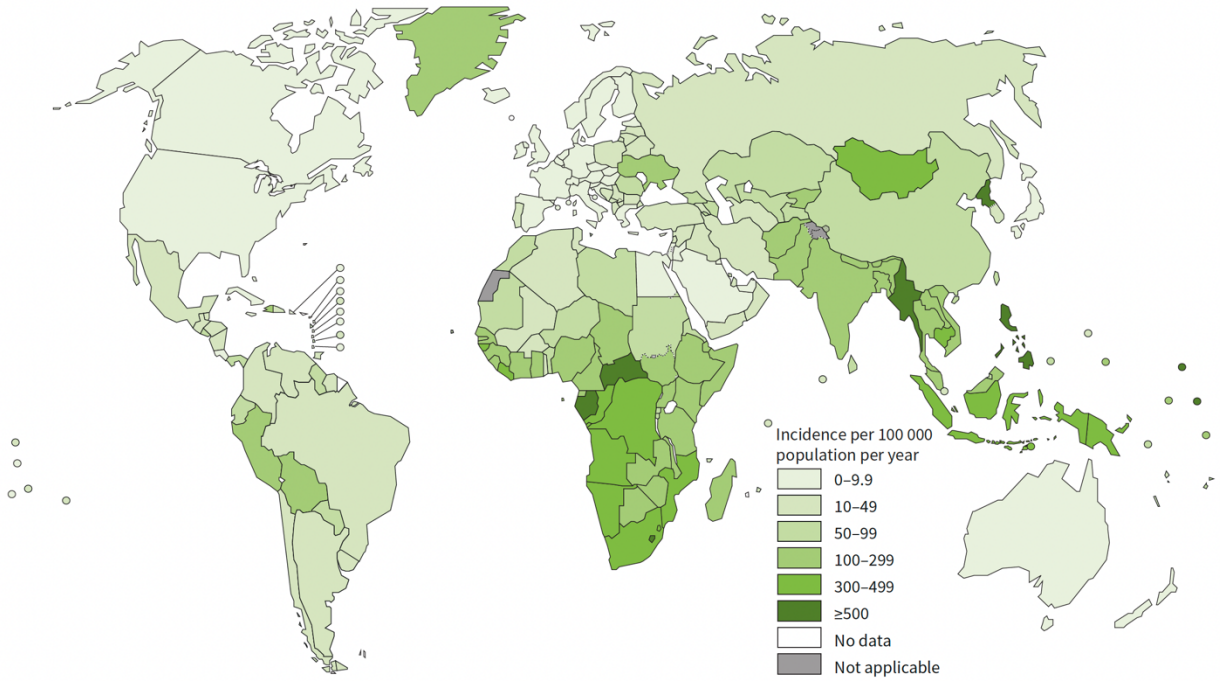
[27]See WHO, "Global Tuberculosis Report," (2024). The estimates made by the IHME are slightly lower: 7,062,668 new cases and 1,290,260 deaths in 2013. See C.J.L. Murray, Theo Vos, and Alan Lopez, "Global, Regional, and National Incidence and Mortality for Hiv, Tuberculosis, and Malaria during 1990–2013: A Systematic Analysis for the Global Burden of Disease Study 2013," *Lancet* 384 (2014)., p. 1035.

[28] WHO, "2024 Global Tb Report," 7.

[29] See *Global Tuberculosis Report* (2019), 27.

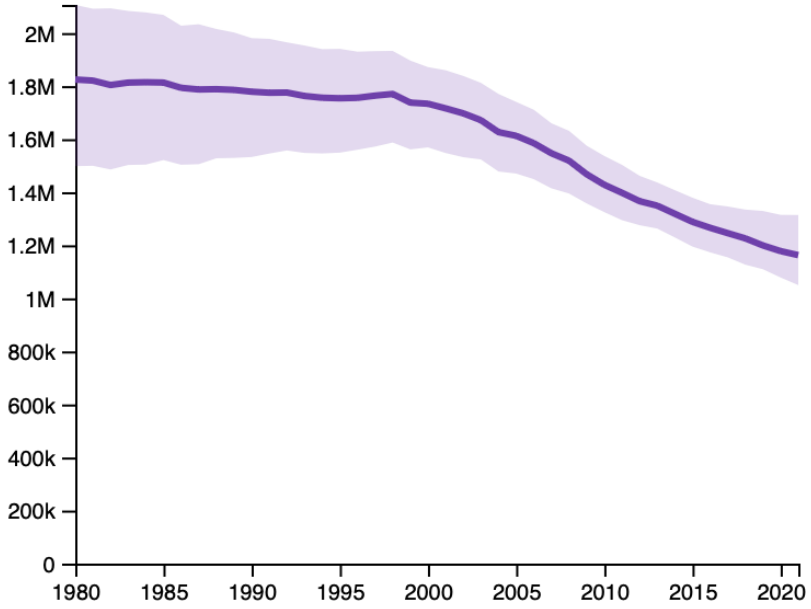
[30] See "2024 Global Tb Report," 9.

Estimated TB incidence rates, 2023



Currently, tuberculosis kills about 1.23 million people per year. Between 1980 and 2019, that number had been steadily declining – first gradually, then more steeply.

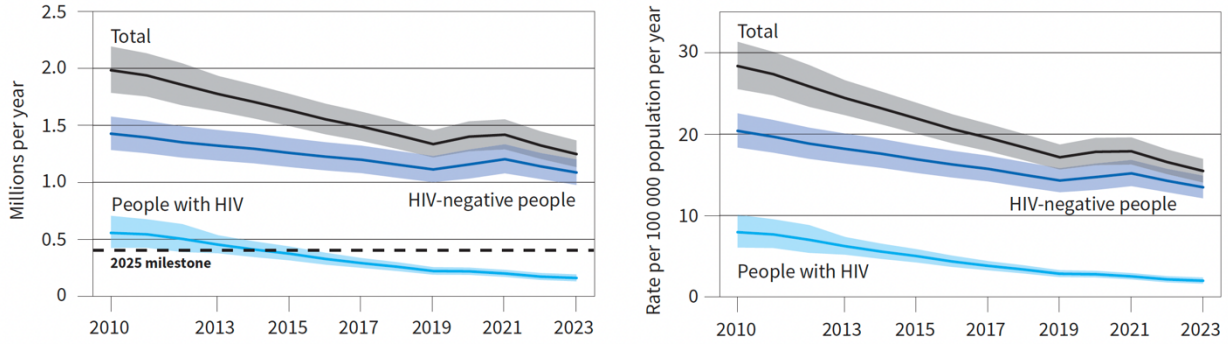
Global Deaths from Tuberculosis[31]



During the pandemic, that number rose significantly, then began to decline again. The figure for 2023 (among HIV-negative people) is approximately the same as the number for 2019.

Global trends in the estimated number of deaths caused by TB (left) and the TB mortality rate (right),[a] 2010–2023

The horizontal dashed line shows the 2025 milestone of the End TB strategy, which is a 75% reduction in the total number of TB deaths between 2015 and 2025. Shaded areas represent 95% uncertainty intervals.



[a] Deaths from TB among people with HIV are officially classified as deaths caused by HIV/AIDS, with TB as a contributory cause.

If successful, two lines of research would go far toward curbing the scourge of TB. First, efforts are currently underway to develop new antibiotics capable of combatting the drug-resistant

[31] Data derived from IMHE, 2021 Global Burden of Disease,

forms of the disease.[32] Two (bedaquiline and delamanid) have recently been approved; ten more are being tested.[33]

Second, various projects are seeking to develop a vaccine that would either be more effective than BCG[34] or would boost the effectiveness of BCG in adults.[35] Currently, six candidates are in phase III trials. Hope is rising that at least one will prove safe and efficacious.[36]

These initiatives are reasonably well funded. Together the NIH, the European Commission, the Gates Foundation, and the Global Alliance for TB Drug Development invest in them more than US$500 million per year.[37] Many pharmaceutical companies and research centers are participating.[38] Thus far, however, the fruits have been disappointing. Although the recently approved drugs and some of those nearing the end of the pipeline offer modest improvements over the existing set of antibiotics, no breakthrough drugs have yet emerged.[39] And, although some of the vaccine candidates have been shown to be safe, none has yet been demonstrated to be effective.[40]

In part, this discouraging result simply reflects the difficulty of the tasks. Finding new safe and effective antibiotics and vaccines of any sort is hard. The projects focused on new TB vaccines face especially high hurdles. Perhaps the most serious is the length of time it takes to test candidates. Because the peak incidence of TB infection occurs in adulthood, and vaccination is

---

[32] See WHO, "Drug-Resistant Tb.", pp. ___.

[33] See Emily B. Wong, Keira A. Cohen, and William R. Bishai, "Rising to the Challenge: New Therapies for Tuberculosis," *Trends in Microbiology* 21, no. 9 (2013).

[34] The two leading candidates for a novel vaccine are recombinant BCG and modified attenuated *M.tuberculosis*. See T. Mark Doherty, *New Vaccines Against Tuberculosis*, TROPICAL MEDICINE AND INTERNATIONAL HEALTH, Vol. 9, No. 7 at 821. Recombinant BCG should theoretically reduce the problem of waning effectiveness over time. See id. Modified attenuated strains of *M.tuberculosis* should mimic the disease-causing bacteria more effectively than modified BCG because BCG is based upon a bovine strain of the TB causing bacteria. *See* S.G. Reed et al., *Prospects for a better vaccine against tuberculosis*, TUBERCULOSIS Vol. 83 at 214 (2003). However, such a vaccine needs to be tested extensively prior to clinical trials to ensure that a return to virulence is not possible.

[35] The concept behind boosting vaccines is that an adjuvated protein vaccine can stimulate BCG into providing immunity later in life, when the vaccine has been demonstrated to become ineffective. *See* T. Mark Doherty, *New Vaccines Against Tuberculosis*, TROPICAL MEDICINE AND INTERNATIONAL HEALTH, Vol. 9, No. 7 at 821. The first phase I human study of a booster TB vaccine began recently, studying the effect of a modified vaccinia virus Ankara expressing Antigen 85 of *M.tuberculosis*. *See* Michael J. Brennan, *The Tuberculosis Vaccine Challenge*, TUBERCULOSIS Vol. 85 at 10 (2005). Two more boosting vaccines will enter human trials in the near future: a Hybrid1 vaccine by the Statens Serum Institute in Denmark and a 72f vaccine from GlaxoSmithKline. *See supra* Doherty at 821. The Statens Serum Institute vaccine is a fusion of ESAT-6 and Ag85B and is scheduled to enter human trials in 2005. *See id.*

[36] See WHO, "2024 Global Tb Report."

[37] *See* Sean Eakins and Antony J. Williams, "Curing Tb with Open Science," *Tuberculosis* 94 (2014).; Doherty at 819 (describing the NIH TB Vaccine Testing and Research Materials Contract, the European Commission-Support TB Vaccine Cluster, and TBVAC and MUVAPRED consortia); R.Glyn Hewinson, *TB Vaccines for the World*, TUBERCULOSIS Vol. 85 at 5 (2005).

[38] For a list, see ibid., 183.

[39] See ibid.; Zhenkun Ma et al., "Global Tuberculosis Drug Development Pipeline: The Need and the Reality," *Lancet* 375, no. 9731 (2010); J.H. Grosset, T.G. Singer, and William R. Bishai, "New Drugs for the Treatment of Tuberculosis: Hope and Reality," *International Journal of Tuberculoisis and Lung Disease* 16, no. 8 (2012).

[40] See Xing, Jeyanathan, and Smaill, "New Approaches to Tb Vaccination."

typically performed upon infants, clinical trials for new drugs may not generate results until decades after they begin.[41] Even the clinical trials for booster vaccines typically span 8-10 years.[42] A limited clinical-testing and manufacturing infrastructure also contributes to slow development of viable TB vaccines.[43] Working with the live pathogens used in attenuated *M.tuberculosis* or recombinant BCG vaccines requires biohazard-level-3 facilities.[44] Not only are such facilities rare and extremely costly to build, they would need to be large enough to produce the vaccine in quantities sufficient for large-scale Phase III human trials and distribution to the subsequent target populations.[45]

Other impediments to drug development, however, are more tractable. The many projects currently underway in various countries are poorly coordinated and rarely share information; the result is needless redundancy in research.[46] Equally important, many projects seem to be languishing in the so-called "valley of death" – the gap between demonstration of promise and satisfaction of the requirements for FDA approval.[47] At least in principle, both obstacles could be removed: the first through more openness and better coordination, the second with money.

In the meantime, the fight against TB must rely on a combination of public-health initiatives (to curtail transmissions) and administration of the existing antibiotics to the patients who are infected by bacteria strains for which those drugs are effective. The latter strategy, however, is hobbled by the high cost in many countries of some of those antibiotics -- in particular the newer drugs that must be deployed to address MDR-TB and XDR-TB. The prices of those drugs contribute importantly to the distressingly high cost and limited availability of treatments for the disease-resistant strains. Whereas the average cost per patient of treating ordinary TB is between US$200 and US$1000 in most countries, the median cost per patient of treating MDR-TB is US$5659 (44% of which consists of the costs of the second-line drugs).[48] The following chart combines information concerning the number of MDR-TB cases treated in each of the high-burden countries with the average costs of treatment in each country:

[41] *See supra* Doherty at 824.

[42] See id.

[43] *See supra* Brennan at 11.

[44] *See id.* at 8.

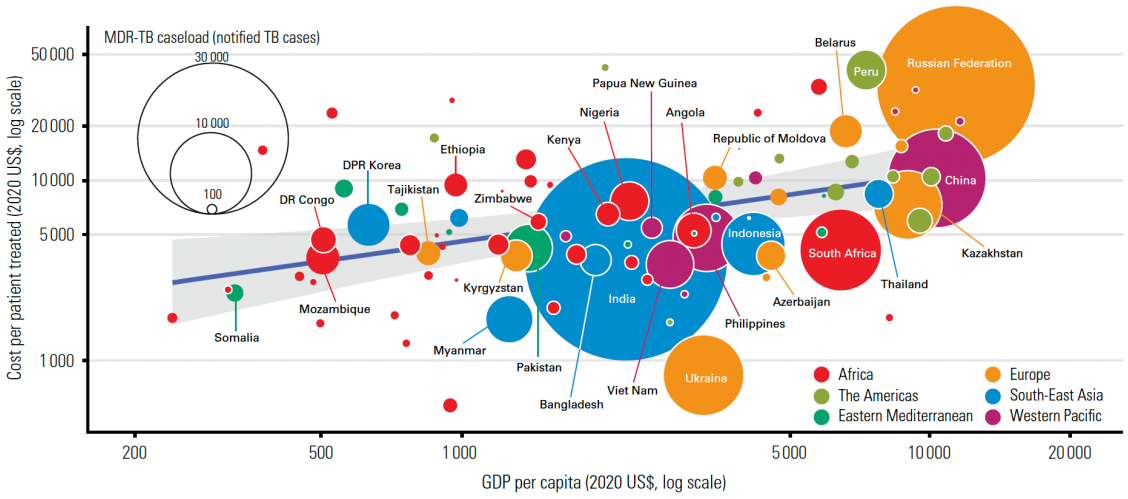
[45] See id.

[46] See Eakins and Williams, "Curing Tb with Open Science," 184.

[47] See Arti K. Rai et al., "Pathways across the Valley of Death: Novel Intellectual Property Strategies for Accelerated Drug Discovery," *Yale Journal of Health Policy, Law, and Ethics* 8 (2008).

[48] See 2019 report, 137

Figure 5[49]



Note that, while the highest costs of treatment are found in Russia and Eastern Europe, the costs in most countries in Africa are not far behind.

These expenses, plus limitations on funding for MDR-TB programs, have had a predictable result: in many countries, waiting lists for MDR-TB treatment are long. Even larger numbers of symptomatic people either have not yet been diagnosed or have been diagnosed but are not yet on waiting lists.[50]

Meanwhile, new varieties of drug-resistant TB continue to proliferate, and the threat they pose to public health intensifies.[51] In 2019, there were roughly half a million new cases of MDR/RR-TB, and 182,000 people died from it.[52] Globally, the percentage of diagnosed TB cases that involve drug resistant varieties has not changed materially in recent years. However, unusually high rates of drug resistance in some countries and the apparent proliferation of varieties that are resistant to *all* drugs are causes for alarm.

Adams, Patrick. "Losing the Fight against Tuberculosis." *New York Times*, January 5, 2015 2015.

Daniel, Thomas M. "The History of Tuberculosis." *Respiratory Medicine* 100 (2006): 1862-70.

de Jong, Bouke C. , Ifedayo Adetifa, Brigitte Walther, Philip Hill, Martin Antonio, Martin Ota, and Richard A. Adegbola. "Diferences between Tuberculosis Cases Infected with Mycobacterium Africanum, West African Type 2, Relative to Euro-American

[49] Source: WHO, "Global Tuberculosis Report," (2020), 142.

[50] See "Global Tb Report.", p. 14.; 2019 report, 97, 100.

[51] For a map showing the global distribution of the genotypes that have been identified thus far, see Dheda et al., "Global Control of Tuberculosis: From Extensively Drug-Resistant to Untreatable Tuberculosis," 322.

[52] See WHO, "2020 Global Tb Report," 55-56.

Mycobacterium Tuberculosis: An Update." *FEMS Immunology & Medical Microbiology* 58 (2010): 102-05.
Dheda, Keertan, Tawanda Gumbo, Neel R. Gandhi, Megan Murray, Grant Theron, Zarir Udwadia, G B Migliori, and Robin Warren. "Global Control of Tuberculosis: From Extensively Drug-Resistant to Untreatable Tuberculosis." *Lancet Respiratory Medicine* 2 (2014): 321-38.
Eakins, Sean, and Antony J. Williams. "Curing Tb with Open Science." *Tuberculosis* 94 (2014): 183-85.
EW, Tiermerma. "Natural History of Tuberculosis: Duration and Fatality of Untreated Pulmonary Tuberculosis in Hiv-Negative Patients: A Systematic Review." *PLoS ONE* 6, no. 4 (2011): e17601.
Grosset, J.H., T.G. Singer, and William R. Bishai. "New Drugs for the Treatment of Tuberculosis: Hope and Reality." *International Journal of Tuberculoisis and Lung Disease* 16, no. 8 (2012): 1005-14.
Keshavjee, Salmaan, and Paul E. Farmer. "Tuberculosis, Drug Resistance, and the History of Modern Medicine." *New England Journal of Medicine* 367 (2012).
Ma, Zhenkun, Christian Lienhardt, Helen McIlleron, and Andrew J Nunn. "Global Tuberculosis Drug Development Pipeline: The Need and the Reality." *Lancet* 375, no. 9731 (2010): 2100-09.
Murray, C.J.L., Theo Vos, and Alan Lopez. "Global, Regional, and National Incidence and Mortality for Hiv, Tuberculosis, and Malaria during 1990–2013: A Systematic Analysis for the Global Burden of Disease Study 2013." *Lancet* 384 (2014): 1005-70.
Rai, Arti K., Jerome H. Reichman, Paul F. Uhlir, and Colin Crossman. "Pathways across the Valley of Death: Novel Intellectual Property Strategies for Accelerated Drug Discovery." *Yale Journal of Health Policy, Law, and Ethics* 8 (2008 2008): 1.
Roy, A, and et al. "Effect of Bcg Vaccination against Mycobacterium Tuberculosis Infection in Children: Systematic Review and Meta-Analysis." *British Medical Journal* 349 (2014).
Volmink, Jimmy, and Paul Garner. "Directly Observed Therapy for Treating Tuberculosis." *Cochrane Database of Systematic Reviews*, no. 4 (2007). http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003343.pub3/abstract;jsessionid=E1CD2AD70A259A19D3DF7F9FB38DC901.f01t02.
WHO. "Drug-Resistant Tb: Surveillance and Response." 2014.
———. "Global Tuberculosis Report." 2020.
———. "Global Tuberculosis Report." (2024).
———. "Global Tuberculosis Report." 2014.
———. *Global Tuberculosis Report.* 2019.
———. "Implementing the Stop Tb Strategy: A Handbook for National Tuberculosis Control Programmes." 2008.
———. "Model List of Essential Medicines." 2013.
———. "The Stop Tb Strategy: Building on and Enhancing Dots to Meet the Tb-Related Millennium Develpment Goals." 2006.
———. *Treatment of Tuberculosis Guidelines.* 4th ed. Geneva2009.
Wong, Emily B., Keira A. Cohen, and William R. Bishai. "Rising to the Challenge: New Therapies for Tuberculosis." *Trends in Microbiology* 21, no. 9 (2013): 493-501.
Xing, Zhou, Mangalakumari Jeyanathan, and Fiona Smaill. "New Approaches to Tb Vaccination." *CHEST* 146, no. 3 (2014): 804.