

Chapter 1: Diseases (version 5.1, August 2021)

This chapter summarizes the epidemiology of six of the infectious diseases that currently afflict the developing world. Three of the six -- tuberculosis, malaria, and HIV/AIDS -- were chosen because of the scale of the harm they cause; each results in the loss of between 35 and 60 million DALYs per year. The fourth, dengue, is a representative example of a “neglected” disease; relatively unknown in developed countries, it is widespread in tropical regions, where it causes modest numbers of deaths but a great deal of suffering. The burdens currently associated with the fifth disease, Ebola, are much lower, but the threat that it and its cousins pose to developing countries is enormous. Last but not least, COVID-19 has already imposed huge burdens on most countries in the world and has begun to devastate developing countries. We examine them in chronological order – in other words, in the sequence in which they came to afflict humans.

Most aspects of the histories of these diseases are discouraging, but not all. Some of the efforts to combat them have been successful – and provide lessons for what more we might do going forward.

As the Introduction made clear, these six are not the only infectious diseases that are currently rampant in the developing world. Each of the others has unique characteristics, some of which will be addressed in the balance of the book. But exploration of this group should suffice to launch our inquiry.

A. Tuberculosis

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 have 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).

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).

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 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 WHO¹²), in which a health-care worker monitors each patient's consumption of the antibiotics,¹³ is intended

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.*

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 Development Goals," (2006).

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

(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 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 (a disease to which we will turn our attention shortly). 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

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 fourth 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 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). See also Figure ___ in the Introduction.

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.

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 Roughly 10 million people develop the active form of disease each year, and 1.45 million die from it.²⁷ 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.²⁸ Figures 1 and 2, below, show the geographic distribution, as of 2019, of new TB infections and of TB mortality rates (excluding the deaths related to HIV).²⁹

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 Smail, "New Approaches to Tb Vaccination," *CHEST* 146, no. 3 (2014).

²⁷ See WHO, *Global Tuberculosis Report* (2019), 27. 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 See WHO, *2019 Global Tb Report*, 27.

²⁹ The figures are derived from "Global Tuberculosis Report," (2020).

Figure 1: Estimated TB Incidence Rates, 2019

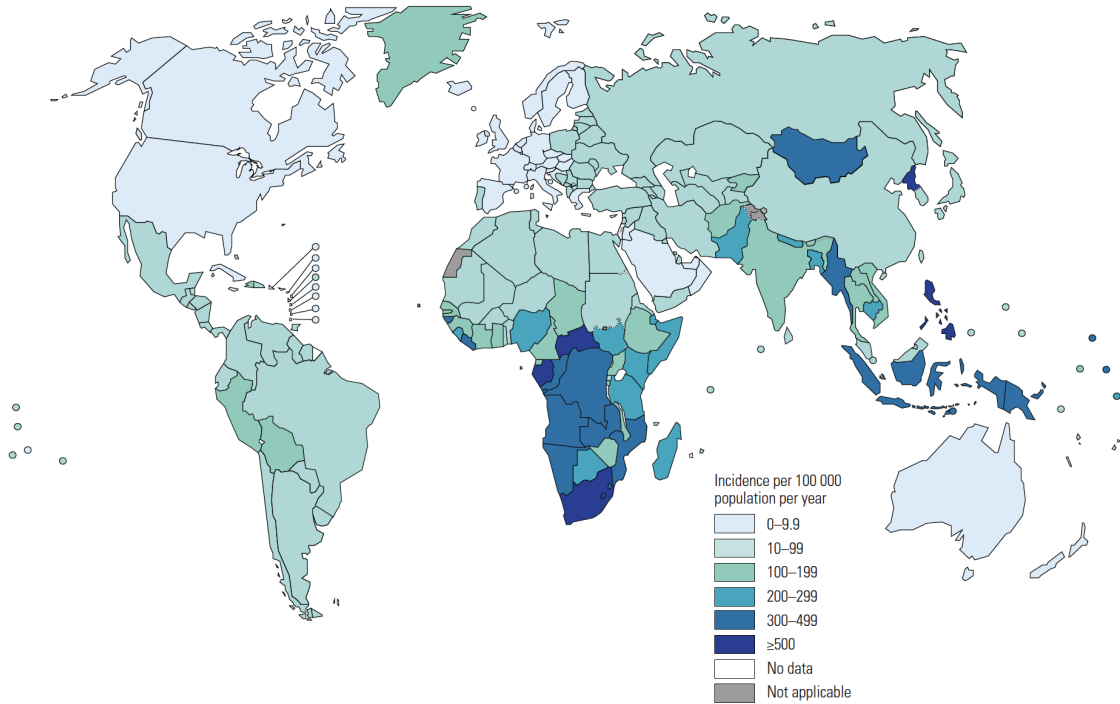
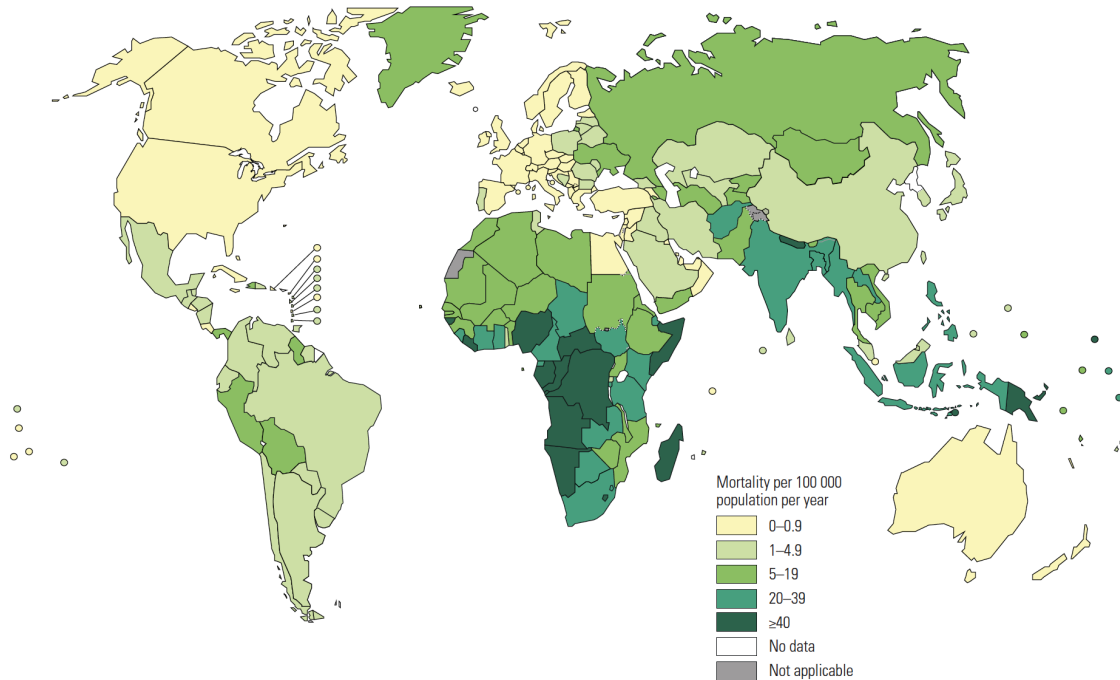


Figure 2: Estimated TB Mortality Rates, 2019 (excluding TB Deaths among HIV-positive people)



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 forms of the disease.³⁰ Two (bedaquiline and delamanid) have recently been approved; ten more are being tested.³¹ Second, various projects are seeking to develop a vaccine that would either be more effective than BCG³² or would boost the effectiveness of BCG in adults.³³ Currently, at least a dozen candidates are in clinical trials.

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.³⁴ Many pharmaceutical companies and research centers are participating.³⁵ 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.³⁶ And, although some of the vaccine candidates have been shown to be safe, none has yet been demonstrated to be effective.³⁷

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 typically performed upon infants, clinical trials for new drugs may not generate results until decades after they begin.³⁸ Even the clinical trials for booster vaccines typically

³⁰ See "Drug-Resistant Tb.", pp. ____.

³¹ 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).

³² 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.

³³ 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.

³⁴ 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).

³⁵ For a list, see *ibid.*, 183.

³⁶ 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 Tuberculosis and Lung Disease* 16, no. 8 (2012).

³⁷ See Xing, Jeyanathan, and Smaill, "New Approaches to Tb Vaccination."

³⁸ See *supra* Doherty at 824.

span 8-10 years.³⁹ A limited clinical-testing and manufacturing infrastructure also contributes to slow development of viable TB vaccines.⁴⁰ Working with the live pathogens used in attenuated *M.tuberculosis* or recombinant BCG vaccines requires biohazard-level-3 facilities.⁴¹ 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.⁴²

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.⁴³ 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. 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).⁴⁴ 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:

³⁹ See *id.*

⁴⁰ See *supra* Brennan at 11.

⁴¹ See *id.* at 8.

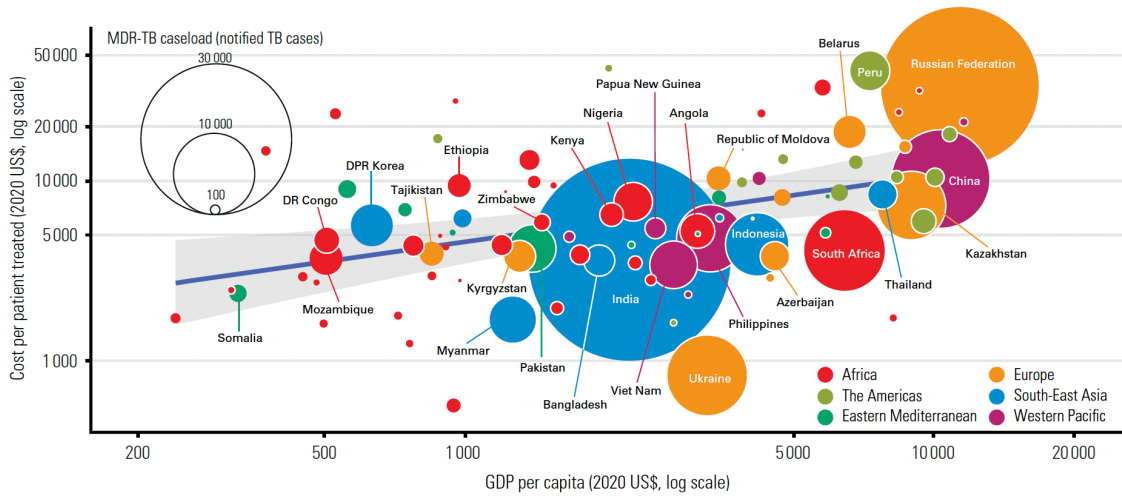
⁴² See *id.*

⁴³ See Eakins and Williams, "Curing Tb with Open Science," 184.

⁴⁴ See 2019 report, 137

Figure 5⁴⁵

Estimated cost per patient treated for MDR-TB in 89 countries,^a 2019



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 either have not yet been diagnosed or have been diagnosed but are not yet on waiting lists.⁴⁶

Meanwhile, new varieties of drug-resistant TB continue to proliferate, and the threat they pose to public health intensifies.⁴⁷ In 2019, there were roughly half a million new cases of MDR/RR-TB, and 182,000 people died from it.⁴⁸ 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.

⁴⁵ Source: WHO, "2020 Global Tb Report," 142.

⁴⁶ See "Global Tb Report," p. 14.; 2019 report, 97, 100.

⁴⁷ 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.

⁴⁸ See WHO, "2020 Global Tb Report," 55-56.

B. Malaria

Malaria infection in a human originates from the bite of a female *Anopheles* mosquito carrying the sporozoite form of *Plasmodium* parasites in her salivary gland.⁴⁹ The sporozoites, deposited under the skin of the host, enter the blood stream and then cross the sinusoidal cellular layer separating the blood and liver parenchyma to infect hepatocytes in the liver.⁵⁰ Temporarily safe from the host's immune response, the sporozoites multiply rapidly to form schizonts, each containing merozoites (a second form of the parasite).⁵¹ The schizonts then rupture, spilling thousands of merozoites into the bloodstream where they invade red blood cells and multiply until the host cells burst.⁵² This cycle continues until "the person dies of anemia, kidney failure, or brain damage, or until the disease is brought under control by the person's immune system or by drugs."⁵³

Because transmission of the disease occurs only through bites from specific species of mosquitos, malaria is common only in countries where those mosquitos flourish. Thousands of years ago, when the disease first emerged, the mosquitos were widely distributed in Eurasia and Africa and thus the disease acquired a large geographic footprint – in temperate areas as well as tropical areas. However, unlike the tuberculosis bacterium, the malaria parasite did not accompany humans across the temporary land bridge between Siberia and the Aleutian peninsula and thus was unknown in the western hemisphere prior to the sixteenth century. Its importation by the European colonists contributed at least modestly to the decimation of the Native American population between the sixteenth and the eighteenth centuries.⁵⁴

As late as 1900, malaria was prevalent in roughly half of the world's land area. Thereafter, the constriction of the zone occupied by *Anopheles* mosquitos (primarily through the widespread use of insecticides and the conversion of swampland to agricultural land) combined with public health-initiatives gradually reduced its footprint. The stages in its retreat are shown in Figure 6.

⁴⁹ See Gina Kolata, *The Search for a Malaria Vaccine*. 226 SCIENCE 679, 680 (November 9, 1984). There are roughly 70 species of *Anopheles* mosquitos, of which roughly 40 play a significant role in transmitting malaria. The differences among them partly account for the variations in the way in which malaria takes form in different parts of the world. For thorough discussion of these variations, see James L.A. Webb, Jr., *Humanity's Burden: A Global History of Malaria* (New York: Cambridge University Press, 2009).

⁵⁰ See Maria M. Mota and Ana Rodriguez, *Migration through host cells: the first steps of Plasmodium sporozoites in the mammalian host*, CELLULAR BIOLOGY Vol. 6, No. 12 at 1113 (2004). The exact mechanism by which sporozoites reach the blood vessel and then cross the blood/liver barrier is unknown, although it is believed that the sporozoites migrate through host cells. See *id.* at 1114.

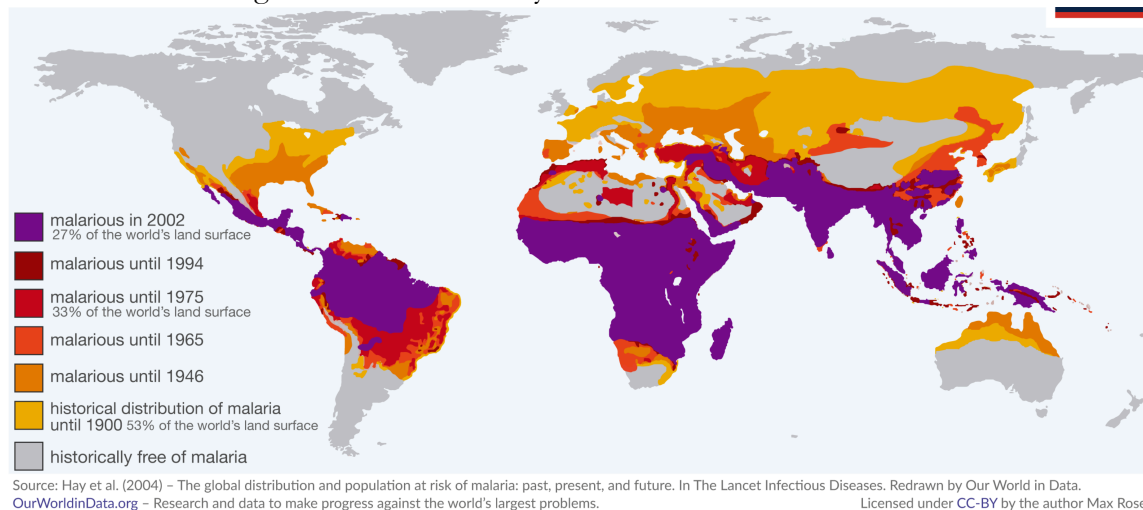
⁵¹ See *supra* Kolata at 680.

⁵² See *id.*

⁵³ *Id.* In developing countries, the majority of malaria deaths occur in infants, young children and pregnant women; most adolescents and adults have developed natural immunity that limits the most severe forms of infection. See Stephen Hoffman, *Save the Children*, NATURE Vol. 430 at 940 (Aug. 19, 2004).

⁵⁴ See Webb, *Humanity's Burden*, 66ff.

Figure 6: Modern History of the Prevalence of Malaria⁵⁵



Currently, five species of the *Plasmodium* parasite are capable of causing the disease: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*.⁵⁶ *P. falciparum*, by far the most lethal, is the dominant species in Africa.⁵⁷ *P. vivax* accounts for roughly half of the cases in Latin American and Southeast Asia,⁵⁸ but is rare in Africa, apparently because most of the people there carry a genetic mutation that renders them immune to *vivax* infections.⁵⁹

As yet, there is only one approved vaccine for malaria, and its effectiveness is modest. In clinical trials, RTS,S/AS01 (developed by GlaxoSmithKline with support from the Malaria Vaccine Initiative) revealed an efficacy of roughly 36% in children and 26% in infants.⁶⁰ That effect was beneficial enough to support approval of RTS,S/AS01 by the EMA and to prompt the WHO in 2019 to initiate pilot projects in Malawi, Ghana, and Kenya to ascertain its potential for reducing childhood mortality.⁶¹ However, the facts that its efficacy diminishes over time and that it shows reduced power when deployed in populations afflicted with

⁵⁵ Source: <https://ourworldindata.org/malaria>.

⁵⁶ See Melanie Figtree et al., "Plasmodium Knowlesi in Human, Indonesian Borneo," *Emerging Infectious Diseases* 16, no. 4 (2010).

⁵⁷ See David Bell and Peter Winstanley, "Current Issues in the Treatment of Uncomplicated Malaria in Africa," *British Medical Bulletin* 71 (2004): 30.

⁵⁸ See Vincent Corbel et al., "Challenges and Prospects for Dengue and Malaria Control in Thailand, Southeast Asia," *Trends in Parasitology* 29, no. 12 (2013).

⁵⁹ "Although *P. vivax* can occur throughout Africa, the risk of infection with this species is quite low, because of the absence in many African populations of the Duffy gene, which produces a protein necessary for *P. vivax* to invade red blood cells." WHO, "World Malaria Report," (2014): 3. See also Webb, *Humanity's Burden*, 21ff.

⁶⁰ See Navneet Arora, Lokhesh C Anbalagan, and Ashok K Pannu, "Towards Eradication of Malaria: Is the Who's Rts,S/As01 Vaccination Effective Enough?," *Risk Management and Healthcare Policy* 14 (2021); P.A. Zimmerman, "Efficacy and Safety of the Rts,S/As01 Malaria Vaccine During 18 Months after Vaccination: A Phase 3 Randomized, Controlled Trial in Children and Young Infants at 11 African Sites," *PLoS Med* 11, no. 7 (2014). Early test results had been more promising. See Pedro L. Alonso et al., Efficacy of the RTS,S/AS02A vaccine against *Plasmodium falciparum* infection and disease in young African children: randomized controlled trial, *THE LANCET* Vol. 364 at 1411 (Oct. 16, 2004).

⁶¹ See Arora, Anbalagan, and Pannu, "Is the Rts,S/As01 Vaccination Effective?," 1037.

multiple variants of the *P. falciparum* parasite limit sharply the public-health benefit to which it will give rise.⁶² Several other research projects are underway, but none is close to developing an effective vaccine.⁶³

In the absence of a robust vaccine, inhibition of the spread of the disease is achieved primarily through vector control: protecting people in malaria-endemic countries against mosquito bites. Two strategies are employed for this purpose: supplying residents with bednets treated with insecticide to shield them from bites while sleeping; and reducing the number of mosquitos in homes by spraying the walls with insecticide. The first of these initiatives has been the most extensive and successful. In the past decade, bednets treated with insecticides (ITNs) have been widely distributed (usually for free) in malaria-endemic countries. Roughly 50% of the population in those countries now sleeps under nets.⁶⁴ They are inexpensive to produce, and their effect is dramatic. Studies suggest that they reduce malaria incidence by half.⁶⁵ The second approach – known as “indoor residual spraying” (IRS) – is equally effective but less widely used; indeed, usage appears to be diminishing, rather than increasing.⁶⁶

Unfortunately, both of these approaches are threatened by increases in the resistance of the pertinent species of mosquitos to the most commonly used insecticides.⁶⁷ To slow the development of this resistance, the WHO recommends that distributors of the chemicals used in IRS and the manufacturers of insecticide treated bed nets rotate the insecticides they employ. Some countries abide by this guideline, but most as yet do not.⁶⁸

Persons who, despite these efforts at vector control, acquire malaria can and should be treated with drugs. Starting in the early nineteenth century, the drug used most often was chloroquine, derived from the bark of a tree native to the Andes and later farmed in parts of Southeast Asia.⁶⁹ In the 1950s, *P. falciparum* parasites began to exhibit resistance to chloroquine, so many health-care systems in regions dominated by that species switched to sulphadoxine-pyrimethamine (SP).⁷⁰ Resistance to SP emerged soon thereafter.⁷¹ Today, most health

⁶² See *ibid.*, 1036; Malaria Vaccine Initiative, "Path and Gsk Welcome Progress toward Rts,S Malaria Vaccine Pilot Implementation with Selection of Countries," (2017), <https://www.malariavaccine.org/news-events/news/path-and-gsk-welcome-progress-toward-rtss-malaria-vaccine-pilot-implementation>.

⁶³ See "Mvi Portfolio," (2019), <https://www.malariavaccine.org/projects/mvi-portfolio>.

⁶⁴ See WHO, "World Malaria Report," (2019), xvi, 28-29, 46-48.

⁶⁵ See Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database of Systematic Reviews, 2004 (2):CD000363 [*recheck]. For slightly less favorable assessments of the efficacy of ITNs, see Mark Musumba, Aklesso Egbendewe-Mondzozo, and Bruce A. McCarl, "Analysis of the Cost of Malaria in Children and Use of Insecticide-Treated Bednets in Africa," *African Development Review* 26, no. 1 (2014).

⁶⁶ See WHO, "2019 Malaria Report," xvi, 48-49.

⁶⁷ See Stephen Hoffman. *Save the Children*, NATURE Vol. 430 at 940 (Aug. 19, 2004); Michelle L Gattton et al., "The Importance of Mosquito Behavioral Adaptations to Malaria Control in Africa," *Evolution* 67, no. 4 (2013).

⁶⁸ See WHO, "Malaria Report 2014," 16-17.

⁶⁹ See Webb, *Humanity's Burden*, 92-126.

⁷⁰ In Central America, where most malaria cases are caused by *P. vivax*, chloroquine remains the drug of choice. Recently, however, some resistance to that drug has been observed, prompting health-care services to shift increasingly toward ACT – described below.

⁷¹ See Bell and Winstanley, "Treatment of Malaria in Africa," 31.

services outside of Latin America use artemisinin-based combination therapy (ACT) as the primary means of treatment.⁷² Artemisinins are remarkably effective. For example, they have been shown to reduce infant mortality caused by malaria by 99%.⁷³

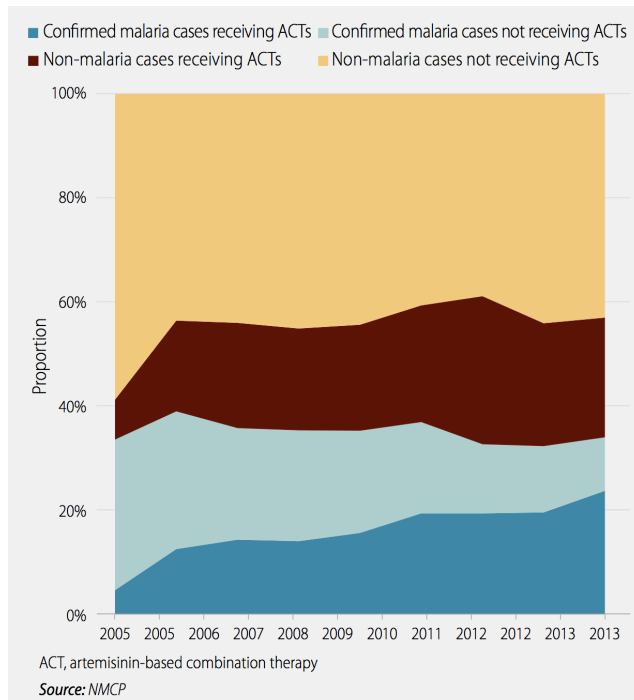
The use of artemisinins has been increasing fast, especially in Africa. The percentage of persons who seek treatment at African public health facilities for malaria-like symptoms who are given ACT has risen sharply since 2005.⁷⁴ Unfortunately, administration of these drugs to people who are not infected by the malaria parasite but instead suffer from other ailments has also grown rapidly.⁷⁵ This has had two bad effects. First, the drugs do those people no good, which causes some of them to lose faith in western medicine and makes them less likely to rely on the health-care system in the future. Second, it accelerates the emergence of strains of the malaria parasites that are resistant to the drugs. Fortunately, artemisinins are less likely than their predecessors to provoke resistance, apparently because they kill off the parasites more rapidly and thus shorten the window for mutation.⁷⁶ But, despite this

⁷² See Robert Ridley, *Winning the Drugs War*, NATURE Vol. 430 at 942 (Aug. 19, 2004). Forty-two malaria endemic countries have switched to ACT. See WHO: *First Global Report on Efforts to Roll Back Malaria*, available at: www.who.int/mediacentre/news/releases/2005/pr17/en/index.html (May 3, 2005). For the WHO's current recommendations concerning their use, see WHO, "Malaria Report 2014," 24.

⁷³ See *ibid.*, 4. The effects on mortality and morbidity of the cycles of drugs and resistance thereto – and the large gains achieved through the switch to ACT – are well illustrated by the recent history of malaria in South Africa. See R Maharaj et al., "Epidemiology of Malaria in South Africa: From Control to Elimination," *South African Medical Journal* 103 (2013).

⁷⁴ See WHO, "2019 Malaria Report," 59.

⁷⁵ The following chart tracks estimated ACT treatment received among malaria and non-malaria cases at public-health facilities in the WHO Africa region. The growth of the dark blue zone is encouraging; the equally dramatic growth of the maroon zone is alarming.



See "Malaria Report 2014," 27.

⁷⁶ See Bell and Winstanley, "Treatment of Malaria in Africa," 32.

advantage, resistance to them is now showing up increasingly often. (The problem is exacerbated by continued sales of oral artemisinin monotherapies [which lead to resistance more quickly than the combination therapies] by some Indian generic companies, despite opposition to the practice by the WHO.⁷⁷)

Pregnant women and infants can be shielded against the active form of malaria through prophylactic administration of the same drugs. A regimen known as “intermittent preventive treatment in pregnancy” (IPTp), which entails periodic administration of SP during the second and third trimesters, has been shown to reduce maternal anaemia, low birth rate, and perinatal mortality.⁷⁸ A similar regimen given to infants (IPTi) substantially reduces anaemia and other manifestations of the disease during the first year of life. A slightly different combination, when given to healthy children between 3 and 59 months old living in areas of highly seasonal malaria transmission, has also proven highly effective.⁷⁹

In the twentieth century, the vector-control programs and the increasingly widespread distribution of ACT drugs, in combination, substantially reduced both the incidence and the mortality of malaria. In recent years, however, progress has slowed. Between 2000 and 2019, the total number of reported cases per year declined only slightly – from 238 million to 229 million. The number of deaths per year fell more sharply – from 736,000 to 409,000, but at a declining pace.⁸⁰ In Africa in particular, the situation is not improving; in 2019, the number of malaria cases was slightly higher than in 2018, and the number of deaths was the same.

The gains, such as they are, have been uneven. The increase in the mortality rate in the Americas in recent years is primarily due to a sharp rise of the rate in Venezuela. And although conditions in some African countries have improved dramatically, in others they have worsened.⁸¹

If we are obliged to rely exclusively on our current disease-control strategies, the chances that we will soon eradicate the disease are not good. Especially worrisome is the recent emergence near the Mekong River of variants of *P. falciparum* that are at least partially resistant to all currently available drugs, including the ACTs.⁸² If the offspring of those parasites reach Africa, millions of people will die. That prospect has prompted some observers to plead for redoubled suppression efforts in Southeast Asia, in hopes of eliminating the deadly variant before it can spread. But purging the disease from the highly mobile populations along

⁷⁷ See WHO, "Malaria Report 2014," 28.

⁷⁸ See *ibid.*, 4; WHO, "Intermittent Preventive Treatment in Pregnancy (Iptp)," (2019), https://www.who.int/malaria/areas/preventive_therapies/pregnancy/en/.

⁷⁹ See "2019 Malaria Report," 14, 21-22.

⁸⁰ See "World Malaria Report," (Geneva 2020), 19.

⁸¹ See Sungano Mharakurwaa et al., "Malaria Epidemiology and Control in Southern Africa," *Acta Tropica* 121 (2012); Abdisalan M Noor et al., "The Changing Risk of Plasmodium Falciparum Malaria Infection in Africa: 2000–10: A Spatial and Temporal Analysis of Transmission Intensity," *The Lancet* 383 (2014).; Huguette Gaelle Ngassa Mbenda, Gauri Awasthi, and Poonam Singh, "Does Malaria Epidemiology Project Cameroon as 'Africa in Miniature?'," *Journal of Bioscience* 39, no. 4 (2014).

⁸² See WHO, "2019 Malaria Report," 68-71.; Mallika Imwong et al., "The Spread of Artemisinin-Resistant Plasmodium Falciparum in the Greater Mekong Subregion: A Molecular Epidemiology Observational Study," *Lancet Infectious Diseases* 17, no. 5 (2017).

the national borders in the region and from the residents of the remote forest villages is a daunting task.⁸³

Once again, therefore, we confront the importance of developing new, more efficacious drugs and, better yet, an effective vaccine. Unfortunately, the obstacles to the discovery, testing, and deployment of a new malaria vaccine are formidable. At least in theory, three strategies are possible. The first approach would attack the sporozoites as they enter the body and invade and reproduce in the liver. Ideally, this kind of vaccine would induce both an antibody and T-cell response, similar to that observed in the development of natural protective immunity. If successful, this type of vaccine would result in complete protective immunity. (This is the strategy employed by RTS,S/AS01, discussed above.) The second approach would limit the invasion of erythrocytes and the subsequent multiplication and pathological effects. This approach would still permit infection, but would prevent at least the more severe outbreaks of the disease. The third approach aims to prevent the spread of viable parasites to other people, thus limiting the potential for an outbreak within a given population. Such vaccines have been labeled “transmission blocking vaccines.” All three approaches are hampered by a common technical problem: Human parasites have much larger genomes than viruses. They also undergo multi-stage life cycles and produce enormous variability in proteins, making the development of an effective single vaccine difficult. The recent completion of the *P.falciparum* genome sequence as well as the genome sequences of model rodent parasites may help scientists to surmount this hurdle, but have not done so yet.⁸⁴

The impediments created by this technical barrier are compounded by some more prosaic difficulties. Clinical trials of vaccine candidates must be performed on infants in communities where malaria is endemic. Persuading mothers, many of whom are illiterate, that they should allow their children to be treated with drugs that have not yet been shown to be safe and effective is no easy task.⁸⁵ But unless we can meet these challenges, we are unlikely to eradicate the disease.

⁸³ See Corbel et al., "Challenges and Prospects for Dengue and Malaria Control in Thailand, Southeast Asia," 631.

⁸⁴ See Patrick E. Duffy et al., Malaria vaccines: using models of immunity and functional genomics tools to accelerate the development of vaccines against Plasmodium falciparum, *VACCINE* Vol. 23 at 2235 (2005); Daniel Carucci, *Know thine enemy*, *NATURE* Vol. 430 at 945 (Aug. 19, 2004). The ability to develop vaccines through newly refined techniques for infecting healthy volunteers may also accelerate research, see Michael F. Good, "The Ability to Inoculate Purified Malaria Sporozoites Will Accelerate Vaccine and Drug Discovery," *American Journal of Tropical Medical Hygiene* 91, no. 3 (2014). – although it is difficult to imagine large numbers of people volunteering for such projects.

⁸⁵ See Muhammed O. Afolabi et al., "Early Phase Clinical Trials with Human Immunodeficiency Virus-1 and Malaria Vectored Vaccines in the Gambia: Frontline Challenges in Study Design and Implementation," *ibid.* 90, no. 5; David I Ojaka et al., "Acceptance of a Malaria Vaccine by Caregivers of Sick Children in Kenya," *Malaria Journal* 13 (2014).

C. Dengue

Like malaria, dengue is transmitted from one person to another by a mosquito – specifically, one of two types of mosquito, *Aedes aegypti* and *Aedes albopictus*.⁸⁶ Unlike malaria, however, it is caused by a virus, rather than a parasite.

The symptoms generated by a dengue infection vary radically. In a majority of the cases, it is not manifested at all. In most of the remainder, it produces a set of symptoms resembling the flu: fever, nausea, skin rash, headaches, and severe joint and muscle pain. This constellation of ailments, commonly known as “dengue fever” or “breakbone fever” is unpleasant and debilitating, but typically lasts only 10 days and results in no permanent impairment.⁸⁷ However, in a small percentage of cases, the disease progresses into the much more dangerous “dengue hemorrhagic fever” (DHF) in which the person’s blood vessels begin to leak plasma into the surrounding spaces in his or her body. If the leakage is severe, it gives rise to “dengue shock syndrome” (DSS), characterized by extremely low blood pressure. If not treated promptly with “vigorous fluid resuscitation,” DSS can be fatal.⁸⁸

There are four closely related strains (or “serotypes”) of the dengue virus.⁸⁹ Infection by one strain confers lifelong immunity to another infection by that strain, but only temporary (roughly two years) of immunity against infection by one of the other strains. A second infection is much more likely to lead to DHF or DSS than a first infection – apparently because of “antibody-dependent enhancement” (ADE), a poorly understood phenomenon.⁹⁰

Like HIV and Ebola, to which we will turn shortly, dengue appears to have originally developed in monkeys.⁹¹ When it made the leap to humans is uncertain. A disease that appeared in China as early as the fourth century A.D. may have been dengue; outbreaks in the French West Indies and Panama in the 17th century and in Indonesia, Egypt, and Philadelphia in the 18th century were probably dengue.⁹² Until World War Two, however, the footprint of the disease was relatively small. Thereafter, various factors caused it to spread increasingly rapidly: the transportation of mosquito pupae in wartime ship cargoes to new regions; urbanization and poverty, which in combination create many small pockets of stagnant water (e.g., plastic bottles; used tires) in which mosquito larvae flourish; the diminution of DDT spraying, particularly in Latin America, after the 1960s, which enabled *aegypti* mosquitos to

⁸⁶ Centers for Disease Control and Prevention, "Epidemiology: Dengue," <http://www.cdc.gov/dengue/epidemiology/>. In rare cases, transmission of the virus may occur through organ transplants or blood transfusions or from mother to fetus across the placental barrier, but the overwhelming majority of transmissions occur via mosquitos. Ibid.

⁸⁷ An excellent description of a typical case can be found in Vanesa Barbara, "10 Days of Dengue Fever," *New York Times*, May 1, 2015.

⁸⁸ See Ngo Thi Nhan et al., "Acute Management of Dengue Shock Syndrome: A Randomized Double-Blind Comparison of 4 Intravenous Fluid Regimens in the First Hour," *Clinical Infectious Diseases* 32 (2001).

⁸⁹ A fifth serotype may have been discovered recently. See Dennis Normile, "Surprising New Dengue Virus Throws a Spanner in Disease Control Efforts," *Science* 342, no. 6157 (2013).

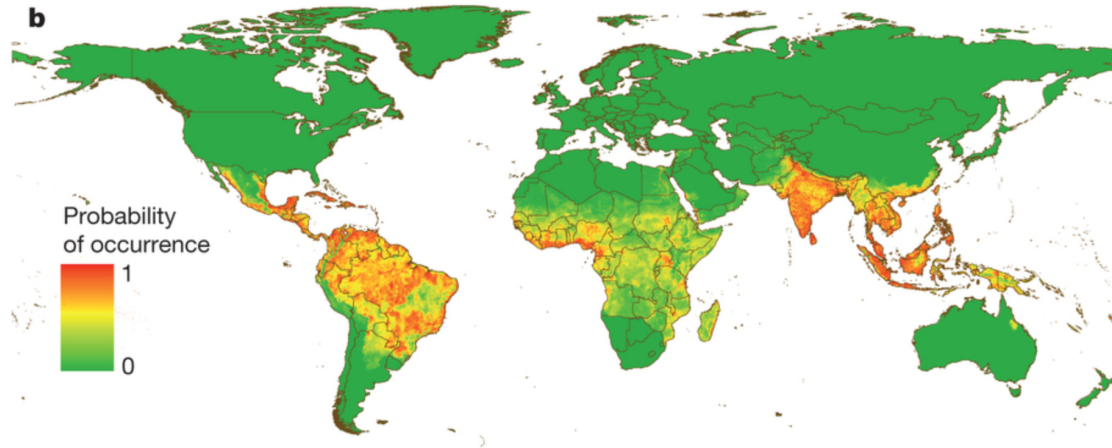
⁹⁰ See Duane Gubler, "Dengue and Dengue Hemorrhagic Fever," *Clinical Microbiology Reviews* 11, no. 3 (1998): 487.

⁹¹ See Maria G. Guzman et al., "Dengue: A Continuing Global Threat," *Nature Reviews Microbiology* (2010): S7.

⁹² See Gubler, "Dengue and Dhf."

rebound; and global warming, which has further increased the range of the relevant mosquitos.⁹³ Figure 7, below, shows the incidence of the disease as of 2010.

Figure 7⁹⁴



As the map makes clear, dengue is now endemic throughout tropical regions of the world. Today, it infects roughly 390 million people per year. Of that number, roughly 96 million experience symptoms of the disease, and 22,000 die. Asia bears the bulk of the burden of the disease. As of 2010, India alone had 34% of the cases, and Asia as a whole had 70%. At that time, only 14% of infections occurred in the Americas (mostly in Brazil and Mexico), but the disease seems to be spreading especially fast in the Western hemisphere. In the (southern) summer of 2015-2016, the number of cases reported in Brazil was triple the number reported during the previous year.⁹⁵ Cases in the United States have thus far been rare, but are likely to increase.⁹⁶

There are, as yet, no effective anti-viral medicines for dengue. Treatment of the disease is therefore “supportive.” Victims of dengue fever are typically advised to rest and drink fluids. Victims of DHF and DSS are provided, when feasible, intravenous rehydration.

⁹³ See *ibid.*

⁹⁴ The map in Figure 1 and, unless otherwise noted, all of the data in the paragraph following Figure 1, have been derived from Samir Bhatt et al., "The Global Distribution and Burden of Dengue," *Nature* 496 (2013). For other maps showing zones in which people are at risk of dengue infections, World Health Organization, http://gamapservr.who.int/mapLibrary/Files/Maps/Global_dengue_2008.png; Pan American Health Organization, <http://www.paho.org/hq/images/stories/AD/HSD/CD/Dengue/2014-cha-distribution-virus-dengue-53.jpg>.

⁹⁵ See Jonathan Gilbert, "Argentina Battles Major Outbreak of Dengue as Mosquito Population Swells," *New York Times*, February 17, 2016; Rogerio Jelmayer, "Brazil Approves Sanofi's Dengue Vaccine," *Wall Street Journal*, December 28, 2015.

⁹⁶ See CDC, "Dengue Cases in the United States" (reporting data as of August 11, 2021, <https://www.cdc.gov/dengue/statistics-maps/2021.html>); Jane P. Messina et al., "Global Spread of Dengue Virus Types: Mapping the 70 Year History," *Trends in Microbiology* 22, no. 3 (2014).; Lorenzo Cattarino et al., "Mapping Global Variation in Dengue Transmission Intensity," *Science Translational Medicine* 12, no. 528 (2020).

Because of the paucity of therapies, efforts to combat dengue are currently focused on two fronts: vector control and the development of a vaccine.⁹⁷ The principal vector-control initiatives are: (a) strategies to reduce the populations of mosquitos, particularly in urban areas;⁹⁸ (b) protecting people against mosquito bites (the same approach used to curb malaria); and (c) reducing the capacity of mosquito bites to transmit the virus.

Efforts to develop a vaccine have been hampered by several factors: the complex pathology of the disease; the necessity of addressing all four of the dengue serotypes; and the difficulty of protecting not just persons who have never been infected, but also persons who have already been infected by one of the four serotypes and thus are at especially high risk for DHF or DSS.⁹⁹ Despite these obstacles, several pharmaceutical firms have been working for decades to develop a vaccine. As of 2010, there were nine such ventures underway;¹⁰⁰ by 2015, there were six.¹⁰¹

The most promising of the candidates was “Dengvaxia,” a live attenuated vaccine developed by Sanofi using a yellow-fever-vaccine backbone. To be sure, Dengvaxia was not perfect. In its stage III clinical trials, it prevented only 61% of infections (albeit a higher percentage of DHF cases) and was less effective in children under nine years old than in adults.¹⁰² But it was sufficiently promising that it was quickly approved for use in Mexico, Brazil, Indonesia, and the Philippines.¹⁰³ Unfortunately, in practice, it proved to have a crucial drawback, which had not come to light in the trials: when administered to a “dengue-naïve” person (i.e., someone who had never been infected by any of the four dengue variants), it produced the ADE effect, mentioned above. In other words, it sharply increased the risk that the person would experience the potentially deadly dengue hemorrhagic fever if subsequently infected with a different variant of the virus. Several patients in the Phillipines died as a result, prompting the government to withdraw its approval of Dengvaxia – and initiate criminal proceedings against Sanofi executives.¹⁰⁴

Dengvaxia has now been approved in other countries, including the United States and parts of the European Union, but only for use on persons who have already undergone at least

⁹⁷ See Guzman et al., "Dengue: A Continuing Global Threat," S12-14.

⁹⁸ See, e.g., Karen Weintraub, "Mosquitos Don't Bug Rich Tourists on Marlon Brando's Island. Here's Why That Matters," *STAT* <http://www.statnews.com/2016/03/03/marlon-brando-mosquitoes/>.

⁹⁹ See Guzman et al., "Dengue: A Continuing Global Threat," S13.

¹⁰⁰ See *ibid.*

¹⁰¹ See Lauren M. Schwartz et al., "The Dengue Vaccine Pipeline: Implications for the Future of Dengue Control," *Vaccine* 33 (2015): 3294.

¹⁰² See Makiko Kitamura, "World's First Dengue Vaccine Approved after 20 Years of Research," *Bloomberg Business*, December 9, 2015.; Monica Antonio, "Dengvaxia, World's First Dengue Vaccine, Gets Mexican Approval -- What You Need to Know," *Patent Herald*, December 11, 2015.

¹⁰³ See Jelmayer, "Brazil Approves Sanofi's Dengue Vaccine.," http://en.sanofi.com/Nasdaq_OMX/local/press_releases/dengvaxia_first_dengue_vaccine_1975899_28-12-201511_30_00.aspx; <http://www.sanofipasteur.com/en/articles/sanofi-pasteur-dengue-vaccine-approved-in-the-philippines.aspx>; <http://www.scidev.net/asia-pacific/disease/news/philippines-licenses-dengue-vaccine-but-usage-on-hold.html>.

¹⁰⁴ See Helen Branswell, "Fda Approves the First Vaccine for Dengue Fever, but with Major Restrictions," *STAT* (2019), <https://www.statnews.com/2019/05/01/fda-dengue-vaccine-restrictions/>.

one Dengue infection.¹⁰⁵ The search continues for a more effective – and widely applicable vaccine.¹⁰⁶

¹⁰⁵ CDC, “Dengue Vaccine,” <https://www.cdc.gov/dengue/prevention/dengue-vaccine.html>; “First FDA-Approved Vaccine for the Prevention of Dengue Disease in Endemic Regions,” May 1, 2019, <https://www.fda.gov/news-events/press-announcements/first-fda-approved-vaccine-prevention-dengue-disease-endemic-regions>.

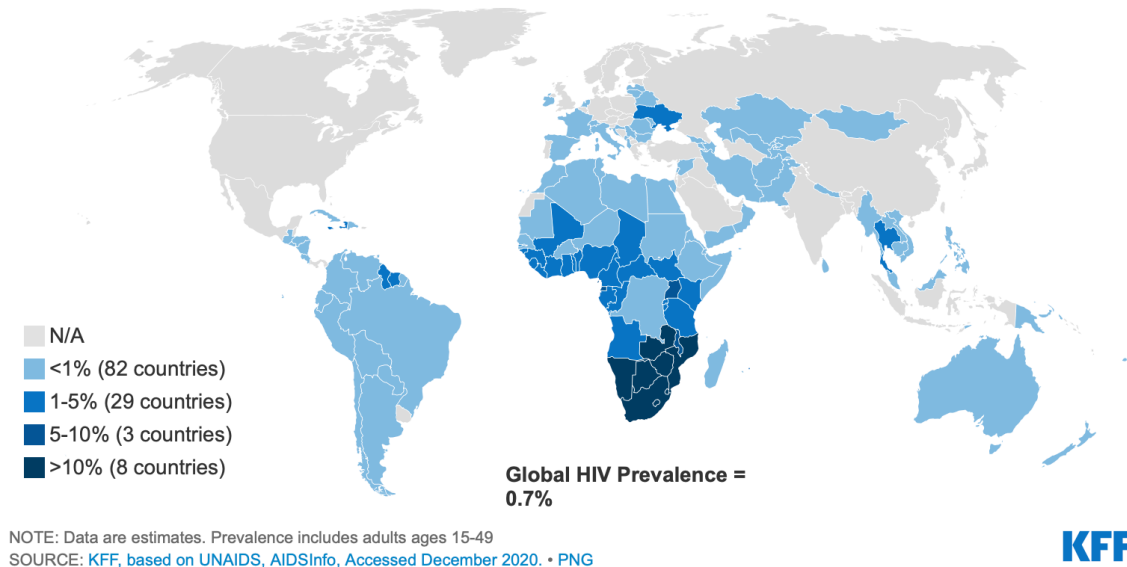
¹⁰⁶ See Sandra Henein et al., “Dengue Vaccine Breakthrough Infections Reveal Properties of Neutralizing Antibodies Linked to Protection,” *Journal of Clinical Investigation* 131 (2021).

D. HIV/AIDS

Like dengue, HIV/AIDS is caused by a virus.¹⁰⁷ It may have been transmitted from chimpanzees to humans in the early 20th century in what is now the Democratic Republic of Congo, but first had a major impact on human populations in the early 1980s. Today, it infects roughly 38 million people in the world.¹⁰⁸ In 2020, 680,000 of them died. This is significantly fewer than the 2.4 million who died during 2005, the peak year of the HIV epidemic, but slightly more than died in 2019.¹⁰⁹ Since 2001, the number of people who are newly infected with HIV each year has been declining, but it is still roughly 1.5 million.¹¹⁰ The result is that the total number of people living with HIV in the world continues to climb.

The adult prevalence of the disease (as of 2019) is shown in Figure 8, below.¹¹¹ As the map indicates, the most adversely affected regions are eastern and southern Africa, where 6.7% of the population is living with HIV.¹¹²

Figure 8: Adult HIV Prevalence, 2019



¹⁰⁷ HIV is a retrovirus, which (unlike most viruses) stores its genetic information in the form of single-stranded RNA, rather than DNA. After it has invaded a host cell, the HIV virus uses an enzyme to generate DNA from the RNA – a process known as “reverse transcription” because ordinarily RNA is “transcribed” from DNA. This modified DNA is then incorporated into the genome of the host cell, after which the virus is perpetuated by the replication of the host-cell DNA. The principal host cells targeted by HIV are CD4+ T lymphocytes and related components of the immune system.

¹⁰⁸ World Health Organization, *HIV/AIDS, Data and Statistics*, <http://www.who.int/hiv/en/>.

¹⁰⁹ See WHO, “Key Facts HIV,” https://cdn.who.int/media/docs/default-source/hq-hiv-hepatitis-and-stis-library/key-facts-hiv-2020.pdf?sfvrsn=582c3f6e_13.

¹¹⁰ Source: UNAIDS, “Fact Sheet - Latest Global and Regional Statistics on the Status of the Aids Epidemic,” (2021).

¹¹¹ Source: KFF, “The Global HIV/AIDS Epidemic” (March 2, 2021), <https://www.kff.org/global-health-policy/fact-sheet/the-global-hiv-aids-epidemic/>.

¹¹² See *ibid.*

HIV is transmitted from one person to another in three main ways: through unprotected sexual relations; through sharing of needles or syringes (typically by intravenous drug users); and from mother to child during pregnancy, birth, or breastfeeding. In the 1980s and '90s, it was also sometimes transmitted through blood transfusions or organ transplants, but these methods are now rare. In many developed countries, the primary form of sexual transmission has been through male-to-male relations, but in developing countries, the primary form has been through heterosexual relations.

The disease caused by HIV typically proceeds through three main phases. Roughly three weeks after transmission, the infected person begins to suffer from symptoms that resemble those associated with influenza: fever, tender lymph nodes, rashes, sores, diarrhea, and so forth. The underlying cause of these symptoms is a sharp drop in the concentration of CD4 lymphocytes in the person's blood and intestinal mucosa and a resultant degradation of her immune system. Roughly nine weeks after transmission, this acute phase of the disease subsides. It is succeeded by a long period of clinical latency, during which the person's CD4 count initially rebounds (in the blood, although not in the mucosa), then very slowly declines. The average duration of the latency period is 8 years, but can be as long as 20 years. Some infected persons never move beyond this phase. In most, however, latency gradually gives way to the set of debilitating and life-threatening symptoms known as AIDS. As the person's CD4 count drops and her immune system deteriorates, she is beset by a growing set of opportunistic infections and viral induced cancers. If untreated, she typically dies within two years.

Various schemas have been developed to mark the progress of the disease. With respect to developing countries, the most influential is the set of four "clinical stages" defined by the World Health Organization. Stage 1 is "asymptomatic" – corresponding roughly to the latency period described above. Stage 2 (CD4 count under 500) is characterized by "mild symptoms" (e.g., recurrent respiratory infections, herpes zoster, fungal nail infections); stage 3 (CD4 count under 350) by "advanced symptoms" (e.g., weight loss, chronic diarrhea, pulmonary tuberculosis, pneumonia); and stage 4 (CD4 count under 200) by "severe symptoms" (e.g., "wasting syndrome," extrapulmonary tuberculosis, Kaposi's sarcoma, disorders of the central nervous system).¹¹³

No cure for HIV/AIDS currently exists. However, since the early 1990s, medicines have become available that can slow or halt the progress of the disease. These medicines are commonly known as "anti-retroviral" drugs (ARVs), less commonly as anti-retroviral therapies (ARTs) or highly active antiretroviral therapies (HAARTs). The most effective are reverse transcriptase inhibitors, which impede the process, described above,¹¹⁴ by which modified DNA is generated from HIV RNA. Inhibitors of this sort include zidovudine (AZT), tenofovir (TDF), lamivudine (3TC), stavudine (d4T), and emtricitabine (FTC).¹¹⁵

¹¹³ For lists of the other symptoms that characterize each stage, see <http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf>, pp. 15-16 (adults) and 17-18 (children).

¹¹⁴ See note ____, above.

¹¹⁵ For a comprehensive catalogue of the ARVs used in developing countries, see MSF, *Untangling the Web of Antiretroviral Price Reductions — 18th Ed.*, (2016), https://msfaccess.org/sites/default/files/HIV_report_Untangling-the-web-18thed_ENG_2016.pdf, pp. 16-46.

Combinations (“cocktails”) of these drugs have proven to be more effective than single drugs; typically, they are administered in combinations of three.¹¹⁶

If a course of these drugs is administered soon enough, it usually slows dramatically the progress of the disease. In some cases, however, the patient either develops resistance to the drugs or suffers increasingly severe side effects. At that point, he or she is usually given so-called “second-line” ARVs. These typically combine previously unused reverse transcriptase inhibitors with protease inhibitors (PIs), which impede the replication of the virus and the release of viral particles from the host cell into the bloodstream.¹¹⁷ If the second-line drugs lose effectiveness, they are replaced by “third-line” ARVs – sometimes called “salvage regimens.”¹¹⁸

Because HIV plagues developed countries as well as developing countries, it has received more attention from researchers, foundations, pharmaceutical firms, and governments than have TB, malaria, or dengue. Much of that attention has focused on vaccine development. Unfortunately, progress has been slow. Researchers face several hurdles: the fact that, in the overwhelming majority of cases, HIV infection does not result in protective immunity, which deprives us of the naturally generated antibodies that are ordinarily employed to design vaccines;¹¹⁹ the genetic diversity among HIV strains and the speed with which the virus evolves in vivo;¹²⁰ and the difficulty of inducing immune protection in the mucosa, where the virus commonly enters the body.¹²¹

Despite these impediments, some progress has been made. Since 2003, five HIV vaccines have shown sufficient promise to warrant clinical trials. The first three candidates failed to show significant efficacy, and the trials were halted. The other two, however, continue to be evaluated. HVTN 705 (Imbokodo), a broad-spectrum candidate, is currently being tested on 2,600 women in five African countries, and HVTN 706 (Mosaico) is being tested on gay men and transgender women in the United States, Latin America and Europe. Results of these trials are expected in 2022 and 2024, respectively. Even if (as is likely) neither candidate

¹¹⁶ For a catalogue of the principal combinations of ARVs, see *ibid.*, pp. 47-69; Clinton Health Access Initiative, “Hiv Market Report: The State of Hiv Treatment, Testing, and Prevention in Low- and Middle-Income Countries,” (2019).

¹¹⁷ PIs that target HIV include saquinavir (developed by Roche), ritonavir (developed by Abbott [renamed AbbVie]), indinavir (developed by Merck), nelfinavir (developed by Agouron Pharmaceuticals and Eli Lilly), and fosamprenavir (a variant of amprenavir, developed by GlaxoSmithKline).

¹¹⁸ See, e.g., Khan et al., Second-line Failure and First Experience with Third-Line Antiretroviral Therapy in Mumbai, India, 7 *Global Health Action* 24861 (2014), available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4119292/pdf/GHA-7-24861.pdf>.

¹¹⁹ See David A. Garber et al., *Prospects for an AIDS Vaccine: three big questions, no easy answers*, *THE LANCET INFECTIOUS DISEASES* Vol. 4 at 397 (July 2004). The significance of this circumstance is suggested by the fact that live-attenuated varicella zoster virus vaccine is the only vaccine ever to be developed for “pathogens that reproducibly establish lifelong infection in their hosts.” *Id.* at 399.

¹²⁰ Several factors have been identified as particularly problematic to the antibody approach to vaccine development: (1) virus particles are difficult to neutralize, (2) the rapid evolution of the virus in vivo, (3) extraordinarily high levels of viral genetic diversity and (4) the down-regulation of MHC-1 molecules on the surface of infected cells. See *id.* at 399.

¹²¹ WHO, “Global Update on the Health Sector Response to Hiv, 2014,” (2014), p. 23.

proves to be the Holy Grail, the trials should help in the development of additional candidates.¹²²

Until an effective vaccine emerges, efforts to halt the AIDS pandemic will continue to focus on reducing the frequency of transmissions of the HIV virus from one person to another. Strategies of these sorts include:

- encouraging use of condoms during sexual relations (which sharply reduces transmissions of the virus);¹²³
- male circumcision (which significantly reduces sexual transmissions from females to males, though not necessarily transmissions from males to females or males to males);¹²⁴
- sexual-abstinence programs (the efficacy of which is as yet unproven);
- providing testing and medical services to sex workers and to intravenous drug users, who are much more likely to be HIV-positive than the general population;¹²⁵
- providing sterile or disposable syringes to intravenous drug users;¹²⁶
- prophylactic administration of ARVs, especially to the infected partners in serodiscordant couples¹²⁷ and to infected pregnant women (which, if begun early enough, nearly eliminates transmission of the virus to their children);¹²⁸
- testing blood supplies, to prevent transmission through infusions;¹²⁹ and

¹²² The long and discouraging story of efforts to develop an effective vaccine is chronicled in Maggie L. Shaw, "The Search for an Hiv Vaccine Continues," *AJMC* (2021), <https://www.ajmc.com/view/the-search-for-an-hiv-vaccine-continues>; NIH, "Experimental Hiv Vaccine Regimen Ineffective in Preventing Hiv," (2020), <https://www.niaid.nih.gov/news-events/experimental-hiv-vaccine-regimen-ineffective-preventing-hiv>; AIDS Vaccine Advocacy Coalition, "Hiv Vaccines: An Introductory Factsheet," (2019).; Miles P. Davenport et al., Predicting the Impact of a Nonsterilizing Vaccine against Human Immunodeficiency Virus, *JOURNAL OF VIROLOGY* Vol. 78, No. 20 (Oct 2004); Khabir Ahmad, New HIV/AIDS vaccine enters phase II trials, *THE LANCET* Vol. 5, at 138 (Mar. 2005).; Edward Nwanegbo et al., Prevalence of Neutralizing Antibodies to Adenoviral Serotypes 5 and 35 in the Adult Populations of The Gambia, South Africa, and the United States, *CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY*, Vol. 11, No.2 at 351 (Mar. 2004); Richard D. Klausner et al., *The Need for a Global HIV Vaccine Enterprise*, *SCIENCE*, Vol. 300 at 2036 (June 27, 2003).

¹²³ See Johnson et al., "The Effect of Changes in Condom Usage and Antiretroviral Treatment Coverage on Human Immunodeficiency Virus Incidence in South Africa," 9 *J R. Soc. Interface* 1544 (2012). The current rates of condom use in the countries where HIV is most prevalent are reviewed in WHO, "Global Update on the Health Sector Response to Hiv, 2014.", pp. 11-12.

¹²⁴ See Auvert, Randomized Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk," 2 *PLoS Med.* E298 (2005); Gray, "Male Circumcision for HIV Prevention in Rakai, Uganda," 369 *Lancet* 657 (2007); Bailey, "Male Circumcision for HIV Prevention in Young Men in Kisumu, Kenya," 369 *Lancet* 643 (2007).

¹²⁵ See WHO, "Global Update on the Health Sector Response to Hiv, 2014.", Table 2.2.

¹²⁶ See WHO, "EFFECTIVENESS OF STERILE NEEDLE AND SYRINGE PROGRAMMING IN REDUCING HIV/AIDS AMONG INJECTING DRUG USERS" (2004), http://www.who.int/hiv/pub/prev_care/effectivenesssterileneedle.pdf?ua=1; WHO, "Best Practices for Injections and Related Procedures Toolkit" (2010), http://www.who.int/injection_safety/toolbox/9789241599252/en/.

¹²⁷ WHO, Note 51

¹²⁸ WHO, "Global Update on the Health Sector Response to Hiv, 2014.", Chpt. 3.

¹²⁹ WHO, Notes 58, 60.

- the use of various precautions by health-care workers, to reduce transmissions from their patients.

Essential both to management of the disease in infected persons and to several of the transmission-prevention programs just described is the availability of ARV drugs. For the first five years after they became publicly available, most of those drugs were subject to patent protection (at least in developed countries), and the companies that held the patents to them charged high prices – typically between US \$10,000 and 15,000 for a year-long course of first-line drugs. These prices placed the drugs beyond the reach of almost all infected persons in developing countries. Starting in 2001, the prices of first-line ARVs in developing countries began to drop sharply. A diverse combination of factors produced the decline: the patents on some of the drugs expired; the efforts of several pharmaceutical firms to prevent South Africa from imposing a compulsory license on their remaining patents produced a public-relations backlash, which in turn prompted the firms to offer to sell their products at low prices in poor countries; generic drug manufacturers in India (where pharmaceutical product patents were not available until recently) began producing ARV cocktails and selling them cheaply in other countries;¹³⁰ the government of Brazil used its bargaining power to extract major price concessions from some of the pharmaceutical firms;¹³¹ the Clinton Foundation (starting in 2002) and UNITAID (starting in 2006) began negotiating contracts with pharmaceutical firms to make cheap ARVs available in developing countries; after 2010, a few other countries (such as Thailand, Indonesia, and Ecuador) followed South Africa's lead in imposing compulsory licenses on ARVs still subject to patent protection; and eventually, some pharmaceutical firms began donating ARVs – or granting generic firms royalty-free licenses to produce them – in poor countries.

The net effect of these disparate forces is that a year-long course of first-line drugs is now available in most low-income countries for less than \$100.¹³² This modest price has, in turn, enabled governments and NGOs (most notably, the President's Emergency Plan for AIDS Relief [PEPFAR] and the Global Fund to Fight AIDS, Tuberculosis and Malaria) to underwrite the cost of the first-line drugs, which in turn has facilitated a radical expansion of the set of people who have access to them.¹³³ The percentage of HIV-positive people throughout the world who now receive ART is roughly 73% (up from 10% in 2006) and rising.¹³⁴

The lessons to be drawn from the ongoing fight against HIV are mixed. Doctors, governments, and philanthropies were inexcusably slow to respond to the threat posed by the

¹³⁰ See AVERT, "Antiretroviral Drug Prices," <http://www.avert.org/antiretroviral-drug-prices.htm>.

¹³¹ See Adele S. Benzaken, Gerson F.M. Pereira, and Lendel Costa, "Antiretroviral Treatment, Government Policy and Economy of Hiv/Aids in Brazil: Is It Time for Hiv Cure in the Country?," *AIDS Research and Therapy* 16, no. 19 (2019).

¹³² See MSF, "Untangling the Web of Antiretroviral Price Reductions," (2020).; WHO, "New High-Quality Antiretroviral Therapy to Be Launched in South Africa, Kenya and over 90 Low- and Middle-Income Countries at Reduced Price," (2019), <https://www.who.int/hiv/mediacentre/news/high-quality-arv-reduced-price/en/>. Tina Rosenberg, "H.I.V. Drugs Cost \$75 in Africa, \$39,000 in the U.S.. Does It Matter?," *New York Times*, September 18, 2018.

¹³³ See Donald G. McNeil, Jr., "Drug Companies Are Focusing on the Poor after Decades of Ignoring Them," *ibid.*, June 24, 2019.

¹³⁴ See UNAIDS, "Fact Sheet - Latest Global and Regional Statistics on the Status of the Aids Epidemic.."

virus. In the past 20 years, however, an enormous amount of resources have been devoted to combatting the disease, many of which have been deployed in developing countries. The fruits of that effort are considerable: AIDS is no longer the leading cause of death in the developing world; first-line ARVs that enable most infected people to live with the disease are now available even in the poorest countries at modest prices; and we may be approaching discovery of a vaccine. On the other side of the ledger, 26% of infected people in the world (and an even higher percentage of infected children) are still not being treated; and second and third-line ARVs (and even some newer first-line ARVs) remain expensive, especially in middle-income countries.¹³⁵ The magnitude of the progress to date is cause for hope – and suggests what could be achieved if comparable resources were brought to bear on other infectious diseases. But the epidemic is far from over; much remains to be done.

¹³⁵ See MSF, "Untangling the Web of Antiretroviral Price Reductions."; Initiative, "Hiv Market Report."

E. Ebola¹³⁶

The list maintained by the World Health Organization of the principal infectious diseases in the world does not include Ebola. The most likely explanation is the disease burden associated with it remains modest. For two reasons, however, we single it out for special treatment. First, although its adverse impact thus far has been modest, the threat that it (and its cousins) pose to global health is severe. Second, the history of efforts to combat Ebola contains important lessons concerning ways in which, in the future, we might combat other infectious diseases.

The Ebola virus is an aggressive pathogen that causes a hemorrhagic shock syndrome in infected humans. Symptoms of that syndrome include fever, headache, fatigue, vomiting, gastrointestinal bleeding, rash, coagulation abnormalities, and a range of hematological irregularities such as lymphopenia (abnormally low levels of lymphocytes) and neutrophilia (abnormally high levels of neutrophil granulocytes).¹³⁷ These symptoms typically first appear 8 to 10 days after exposure to the virus.¹³⁸ If untreated, they usually result in death 6 to 9 days later. Infected pregnant women often suffer abortion, and infants born to mothers dying of the infection typically are themselves infected.¹³⁹

Key to the virulence of the virus is its surface glycoprotein, which mediates viral entry into host cells.¹⁴⁰ The protein allows the virus to introduce its contents into monocytes and/or macrophages (white blood cells), where cell damage or exposure to viral particles triggers the secretion of inflammatory cytokines (also known as a cytokine storm or exaggerated inflammatory response), leading to intravascular coagulation, vascular collapse, and multiple organ failure.¹⁴¹

The life cycle of the Ebola virus is as yet poorly understood. Its principal long-term, tolerant host appears to be the fruit bat, which lives in the forests of central Africa. Active Ebola infection has been detected in three species of bats, and antibodies have been detected

¹³⁶ An early draft of a paper containing the following description of Ebola was prepared for a workshop, hosted by Global Access in Action, held at Harvard University on July 10, 2015. (A list of the workshop participants may be found at <http://www.globalaccessinaction.org/files/2015/06/GAiA-workshop-draft-participant-list-16-06-25.pdf>; for information concerning Global Access in Action, see <http://www.globalaccessinaction.org>.) The discussion at the workshop were helpful in revising the paper, as were written comments submitted by Justin Hughes, Michael Kurilla, Helene Madonick, Quentin Palfrey, Diane Rosenfeld, Judit Rius Sanjuan, and Mark Wu.

¹³⁷ See N. Sullivan, "Ebola Virus Pathogenesis: Implications for Vaccines and Therapies," *Journal of Virology* 77, no. 18 (2003).

¹³⁸ CDC, "Ebola – Signs and Symptoms," <http://www.cdc.gov/vhf/ebola/symptoms/index.html> (last visited June 12, 2015).

¹³⁹ See B. Beer and R. Kurth, "Characteristics of Filoviridae: Marburg and Ebola Viruses," *Naturwissenschaften* 86 (1999).

¹⁴⁰ See J. Ledgerwood, "Chimpanzee Adenovirus Vector Ebola Vaccine – Preliminary Report," *New England Journal of Medicine* (2014).

¹⁴¹ See Sullivan, "Ebola Virus Pathogenesis."; N. Wauquier, "Human Fatal Zaire Ebola Virus Infection Is Associated with an Aberrant Innate Immunity and with Massive Lymphocyte Apoptosis," *PLOS Neglected Tropical Diseases* (2010).

in 6 other species.¹⁴² Monkeys and apes occasionally become infected by the virus, probably by eating fruit on which the bats have gnawed. Humans apparently acquire the virus either through contact with bats or by eating the meat of infected bats or monkeys.¹⁴³ Infections are then transmitted from one person to another through direct contact with: the blood or body fluids of an infected person or corpse; needles or syringes that have been contaminated with body fluids from an infected person; or possibly semen from a man who has recovered from Ebola.¹⁴⁴ Currently, the most effective way to halt the spread of the disease is to prevent all such direct contacts. This is typically achieved by isolating infected persons and by ensuring that all health-care providers who come into contact with them wear personal protective equipment.

The disease was first discovered in 1976. Since then, there have been 24 documented outbreaks in humans. Details concerning those outbreaks are presented in the following table and accompanying map.¹⁴⁵

¹⁴² The three principal species are *Epomops franqueti*, *Hypsignathus monstrosus*, and *Myonycteris torquata*. Insectivorous free-tailed bats (*Mops condylurus*) may also be carriers. See A. Saéz et al., “Investigating the zoonotic origin of the West African Ebola epidemic”, *EMBO Molecular Medicine*, December 30, 2014, available at: <http://embomolmed.embopress.org/content/early/2014/12/29/emmm.201404792>; Morin, M. “Insect-eating bats, not fruit bats, sparked Ebola outbreak, study says”, *Los Angeles Times*, December 30, 2014, available at: <http://www.latimes.com/science/sciencenow/la-sci-sn-ebola-bat-20141230-story.html>.

¹⁴³ CDC, “Ebola – Transmission,” <http://www.cdc.gov/vhf/ebola/transmission/index.html>, (last visited June 12, 2015); Saéz et al., “Investigating the zoonotic origin.”

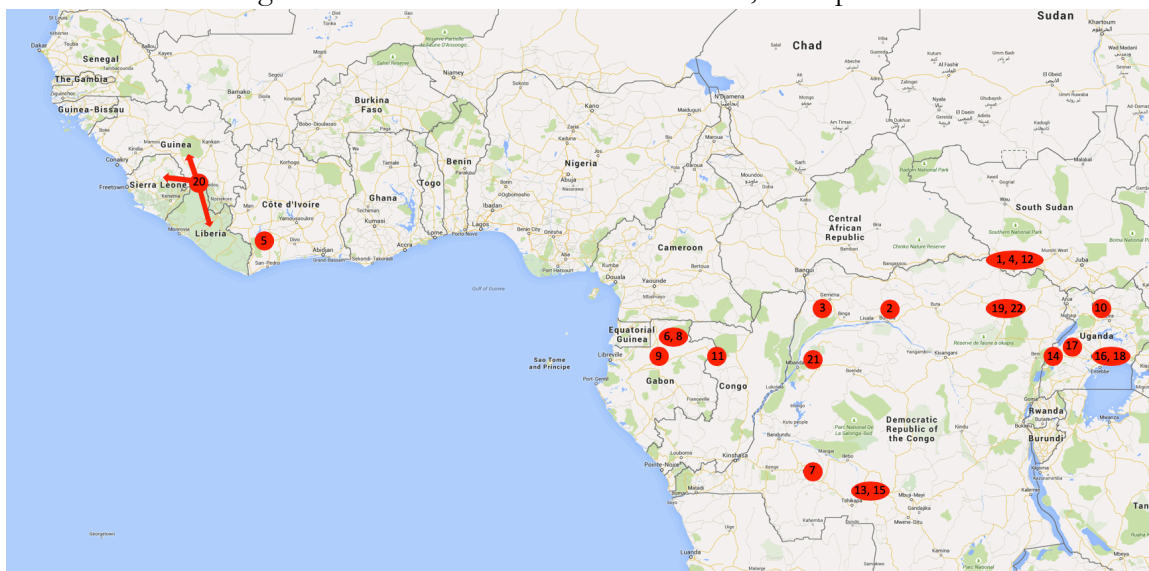
¹⁴⁴ CDC, “Ebola – Transmission”; Gibrilla Deen et al., *New England Journal of Medicine*, Oct. 14, 2015. There is no evidence that the virus is transmitted through the air or water – or via insects.

¹⁴⁵ The sources for these data are: “A History of Ebola in 24 Outbreaks,” *New York Times*, <http://www.nytimes.com/interactive/2014/12/30/science/history-of-ebola-in-24-outbreaks.html>; Healix International, History of Ebola, <http://www.healix-international.com/ebola/history-of-ebola/>; CDC, “2014 Ebola Outbreak in West Africa – Case Counts,” <http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html> (last visited August 28, 2015); the WHO’s Ebola Situation Reports, available at <http://apps.who.int/ebola/ebola-situation-reports> (last visited August 18, 2021); and WHO, “Cote D’Ivoire Declares First Ebola Outbreak in More Than 25 Years.” The total number of outbreaks is disputed, primarily because some researchers regard a series of infections in one location (e.g., along the Congo/Gabon border) as a single outbreak, while others treat them as distinct.

Figure 9: Ebola Outbreaks, 1976-present

	Location	Dates	Species	Cases	Deaths	Fatality Rate
1	Nzara, Sudan	1976	Sudan	284	151	53%
2	Yambuku, Zaire	1976	Zaire	318	280	88%
3	Bonduni, Zaire	1977	Zaire	1	1	100%
4	Nzara, Sudan	1979	Sudan	34	22	65%
5	Tai National Park, Ivory Coast	1994	Tai Forest	1	0	0%
6	Mékouka, Gabon	1994-1995	Zaire	52	31	60%
7	Kikwit, Zaire	1995	Zaire	315	254	81%
8	Mayibout, Gabon	1996	Zaire	31	21	68%
9	Mvounou, Gabon	1996-1997	Zaire	61	46	75%
10	Gulu, Uganda	2000-2001	Sudan	425	224	53%
11	Congo/Gabon border	2001-2005	Zaire	314	264	85%
12	Yambio, Sudan	2004	Sudan	17	7	41%
13	Bamoukamba, Democratic Republic of Congo (DRC)	2007	Zaire	264	187	71%
14	Kabango, Uganda	2007	Bundibugyo	149	37	25%
15	Luebo, DRC	2008	Zaire	32	14	44%
16	Nakisamata, Uganda	2011	Sudan	1	1	100%
17	Nyanswiga, Uganda	2012	Sudan	24	17	71%
18	Luwero, Uganda	2012	Sudan	7	4	57%
19	Isiro, DRC	2012	Bundibugyo	57	29	51%
20	Guinea; Sierra Leone; Liberia	2013-2015	Zaire (Makona strain)	28,490	11,312	40%
21	Equateur, DRC	2018	Zaire	54	33	61%
22	Kivu, DRC	2018-present	Zaire	3,313	2,203	66%
23	Guinea	Feb-June, 2021		23	12	52%
24	Cote d'Ivoire	August 2021				

Figure 10: Locations of Ebola Outbreaks, 1976-present



As the table suggests, several species of the Ebola virus have been identified, each of which has several distinct strains.¹⁴⁶ Three of the species – commonly known as the Zaire, Sudan, and Bundibugyo versions – are especially dangerous to humans. The highest fatality rate is associated with the Zaire version.¹⁴⁷ Its rapid progression provides little opportunity to develop natural immunity; its unusually high replication rate overwhelms the protein-synthesis apparatus of infected cells and host immune defenses.¹⁴⁸

As the table also reveals, the 20th outbreak – commonly known as the “West African Outbreak” – was by far the most serious. The “index case” for this outbreak was Emile Ouamouno, a two-year old boy from the remote Guinean village of Meliandou, who died shortly after manifesting symptoms of fever, headache, and bloody diarrhoea. His death was soon followed by those of his sister and mother. Inadequate communications infrastructure, ignorance of the virus, contact-heavy burial rituals, and porous national borders helped the virus spread rapidly, giving rise to a devastating outbreak that killed more than 5,000 people in its first year, leaving hundreds of children orphaned and affecting thousands more.¹⁴⁹ By the end of March 2014, the virus had spread to Liberia. Within a few months, it had spread to Sierra Leone, Nigeria, Senegal, and Mali.¹⁵⁰ A few cases were also reported in Germany, Norway, France, Italy, Switzerland, the United States, and the United Kingdom – most involving medical workers who had contracted the virus in West Africa and then returned

¹⁴⁶ For a comprehensive list of the species and strains – and links to maps of the DNA of each – see Virus Pathogen Resource, “Ebolavirus,” available at http://www.viprbrc.org/brc/home.spg?decorator=filo_ebola (last visited June 29, 2015).

¹⁴⁷ See Wauquier, “Human Fatal Zaire Ebola Virus Infection.”

¹⁴⁸ See Sullivan, “Ebola Virus Pathogenesis.”

¹⁴⁹ See N. Stylianou, “How World’s Worst Ebola Outbreak Began with One Boy’s Death,” *BBC News*, 27 November 2014.

¹⁵⁰ BBC, “Ebola: Mapping the outbreak,” updated 5 June 2015, available at: <http://www.bbc.com/news/world-africa-28755033>

home.¹⁵¹ By the spring of 2015, the virus had infected over 27,000 people and claimed over 11,000 lives.¹⁵²

Prior to the West African outbreak, there existed no effective vaccine or antiviral therapy for Ebola.¹⁵³ This was not because the development of one or the other would have been unduly difficult or expensive. Indeed, as early as 2005, a group of Canadian researchers had already developed an extremely promising vaccine candidate.¹⁵⁴ The researchers recommended that clinical trials of the two vaccine candidates begin promptly. Unfortunately, this never occurred. The result is that, when the West African Outbreak bloomed, public health officials were poorly equipped to suppress it.

The scale of the 2015 outbreak – and the threat it seemed to pose, not just to the residents of West Africa, but to the rest of the world – suddenly focused attention on Ebola. Several pharmaceutical firms commenced or revived projects to develop vaccines or therapies. Agencies of the governments of several wealthy countries contributed substantial supplementary funding to those projects. In December of 2014, the United States Congress, spurred by the Obama Administration, adopted the *Adding Ebola to the FDA Priority Review Voucher Program Act*.¹⁵⁵ The new law permits vouchers for neglected tropical diseases to be used just 90 days after a company notifies the FDA of its intent to file a new drug, whereas previously notification was required 365 days in advance. The law also permits tropical vouchers to be resold an unlimited number of times, whereas previously only one sale was

¹⁵¹ Ibid.

¹⁵² See "The Toll of a Tragedy," *The Economist*, May 5, 2015. As bad as the West African Outbreak was, it easily could have been much worse. The most severe threat occurred in Nigeria. In the summer of 2014, Patrick Sawyer (an American of Liberian descent), who was already seriously ill with Ebola, flew from Liberia to Lagos. Although he was taken immediately to a hospital, he died soon thereafter, as did four of the doctors and nurses who tried to treat him and some other people who visited him. See Nick Cumming-Bruce, "Nigeria Is Free of Ebola, Health Agency Confirms," *New York Times*, October 20, 2014. Conditions were ripe for an "apocalyptic urban outbreak." WHO, "Nigeria is Now Free of Ebola Virus Transmission," 20 October 2014, <http://www.who.int/mediacentre/news/ebola/20-october-2014/en/>. 21 million people live in Lagos, most of them poor and transient. Had the virus gotten loose in that population, the result would have been catastrophic. That it did not was largely attributable to an extraordinarily aggressive public-health initiative (including 18,000 face-to-face visits), which succeeded in identifying and isolating all of the persons who came into contact with the first and second tiers of victims. See Donald C. McNeil, Jr., "Nigeria's Actions Seem to Contain Ebola Outbreak," *ibid.*, September 30, 2014. Disaster was thus avoided – but barely.

¹⁵³ See N. Sullivan, "Development of a Preventive Vaccine for Ebola Virus Infection in Primates," *Nature*, November 30, 2000.

¹⁵⁴ Steven M Jones et al., "Live Attenuated Recombinant Vaccine Protects Nonhuman Primates against Ebola and Marburg Viruses," *Nature Medicine* 11 (2005). The abstract of this article makes clear how far the research had gone: "Vaccines and therapies are urgently needed to address public health needs stemming from emerging pathogens and biological threat agents such as the filoviruses Ebola virus (EBOV) and Marburg virus (MARV). Here, we developed replication-competent vaccines against EBOV and MARV based on attenuated recombinant vesicular stomatitis virus vectors expressing either the EBOV glycoprotein or MARV glycoprotein. A single intramuscular injection of the EBOV or MARV vaccine elicited completely protective immune responses in nonhuman primates against lethal EBOV or MARV challenges. Notably, vaccine vector shedding was not detectable in the monkeys and none of the animals developed fever or other symptoms of illness associated with vaccination. The EBOV vaccine induced humoral and apparent cellular immune responses in all vaccinated monkeys, whereas the MARV vaccine induced a stronger humoral than cellular immune response. No evidence of EBOV or MARV replication was detected in any of the protected animals after challenge. Our data suggest that these vaccine candidates are safe and highly efficacious in a relevant animal mode."

¹⁵⁵ See <https://www.congress.gov/113/plaws/publ233/PLAW-113publ233.pdf>.

permitted. Because the market value of such a readily transferrable voucher generally exceeds \$100 million, this significantly amplified the financial incentives for private firms to develop Ebola vaccines.¹⁵⁶ (In Chapter 7, we will examine this statute in more detail.)

The results were impressive. 12 vaccine candidates and 9 therapy candidates quickly emerged from this surge of activity and investment. Accelerated deployment of the most promising vaccine (rVSV-ZEBOV, derived from the candidate identified by the Canadian researchers) soon demonstrated its effectiveness. The vaccine was then used to inoculate persons who might have come into contact with people infected by the virus, and the rates of new infections rapidly dropped. When the next outbreak occurred, in a western province of the Congo, rapid administration of rVSV-ZEBOV to 3481 people helped keep the numbers of infections and deaths low.¹⁵⁷

The outcome of this story is not entirely happy, however. As the persistent outbreaks in various locations in West Africa make clear, possession of an effective vaccine will not be sufficient to eliminate the disease. In part, this is because the vaccine must be administered to people at risk – no easy task in rural subSaharan Africa, particularly in regions beset by violence.¹⁵⁸ In addition, rVSV-ZEBOV is only effective against one strain of the Ebola virus. As yet, we have no approved vaccines against the other strains – or against the close cousins of Ebola, some of which are at least as dangerous. For example, the Marburg virus, similar to Ebola, has recently been found in bats in Sierra Leone.¹⁵⁹ Although one of the scientists involved in the development of rVSV-ZEBOV has developed a vaccine for Marburg, it has not yet been tested in humans.¹⁶⁰

¹⁵⁶ Confirmation of this common estimate comes from the fact that, after the Canadian company Knight Therapeutics received a PRV for its leishmaniasis treatment, it sold the voucher to Gilead Sciences for \$125 million. See A. Gaffney, "Regulatory Explainer: Everything You Need to Know About Fda's Priority Review Vouchers," *Regulatory Affairs Professionals Society*, 28 May 2015.

¹⁵⁷ See J. Daniel Kelly et al., "Projections of Ebola Outbreak Size and Duration with and without Vaccine Use in Equateur, Democratic Republic of Congo, as of May 27, 2018," *PLoS One* 14, no. 3 (2018). (predicting, accurately, the effectiveness of the vaccine in controlling the Equateur outbreak) .

¹⁵⁸ The following description of the conditions in the eastern Congo, the site of the most serious recent outbreak, suggests the challenges confronted by health-care workers: "There is almost no functioning state in much of eastern DRC. There is an almost total lack of basic services such as power, education, roads, healthcare, and the authority of the government only extends to the edges of urban areas.... Most people in the region live hand to mouth, growing their own vegetables or scraping enough to make a living from day labour, gathering wood for charcoal and a small amount of trade. Police are corrupt, predatory and violent. In rural zones, militia and armed bands provide security and employment opportunities but also steal, rape and kill at will. It is one of the most hostile environments faced by aid and health workers anywhere in the world." Sarah Boseley and Jason Burke, "Ebola in the Drc: Everything You Need to Know," *The Guardian* (2019), <https://www.theguardian.com/world/2019/may/15/ebola-in-the-drc-everything-you-need-to-know>.

¹⁵⁹ See, e.g., Centers for Disease Control, "About Marburg Hemorrhagic Fever," (2014), <https://www.cdc.gov/vhf/marburg/about.html>; Maggie Fox, "Deadly Ebola Cousin Marburg Found in West African Bats," *NBC News* (2018), <https://www.nbcnews.com/health/health-news/deadly-ebola-cousin-marburg-found-west-african-bats-n950331>.

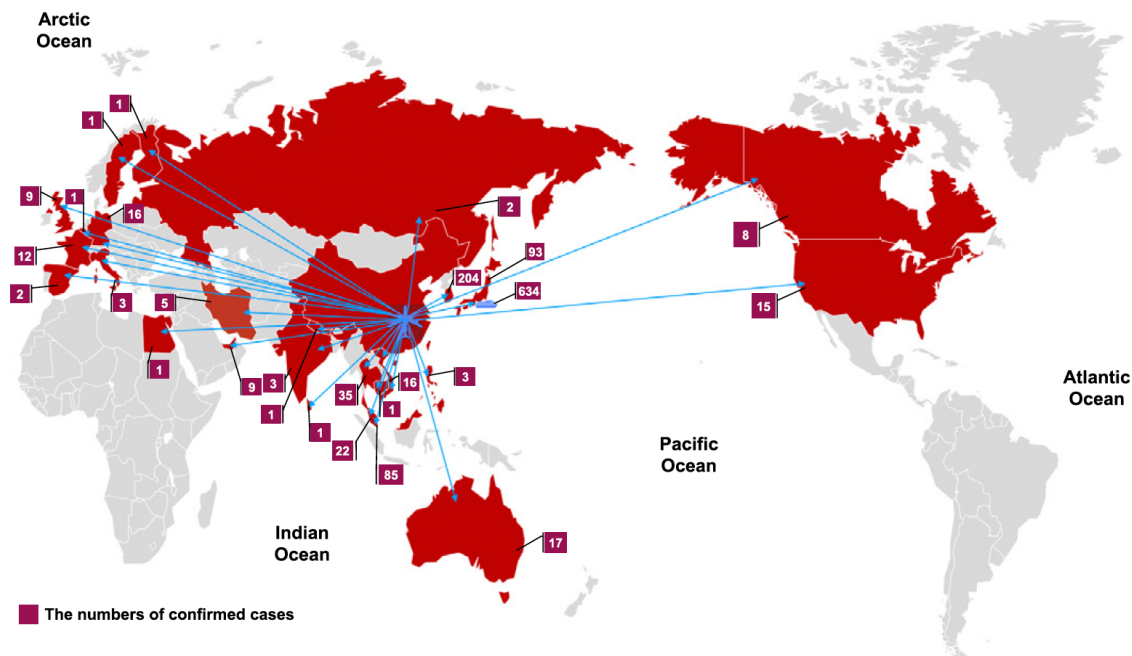
¹⁶⁰ See Alexandra Becker, "Marburg Virus, a Cousin to Ebola, Has Been Found in Bats in West Africa," *TMC News* (2019), <https://www.tmc.edu/news/2019/01/marburg-virus-a-cousin-to-ebola-has-been-found-in-bats-in-west-africa/>.

F. COVID-19

The last of the six diseases is undoubtedly the most familiar to most readers. We will summarize its epidemiology briefly, concentrating on those aspects most relevant to the project of this book.

In December of 2019, a small group of people in Wuhan City, China, contracted a hitherto unknown disease. Exactly how they acquired it remains uncertain (and sharply contested), but the leading explanation is that one or more of them came into contact with an infected wild animal in an outdoor “wet” market.¹⁶¹ The disease proved to be highly infectious and soon spread rapidly through the population of the city. In January of 2020, cases began to appear in other cities in China and then in other countries to which residents of (or visitors to) Wuhan had traveled.¹⁶² The footprint of the disease two months after its initial appearance is shown below.

Figure 11: The Spread of COVID-19 as of February 20, 2020¹⁶³



¹⁶¹ For some of the contributions to the ongoing debate over the origins of the pandemic, see Kristian G. Andersen et al., "The Proximal Origin of Sars-Cov-2," *Nature Medicine* 26 (2020); Jesse D. Bloom et al., "Investigate the Origins of Covid-19," *Science* (2020), <https://science.sciencemag.org/content/372/6543/694.1>; Edward C; Holmes et al., "The Origins of Sars-Cov-2: A Critical Review," (2021), <https://zenodo.org/record/5112546#.YSTUdS-cYxk>; Xiao Xiao et al., "Animal Sales from Wuhan Wet Markets Immediately Prior to the Covid-19 Pandemic," *Scientific Reports* 11 (2021); Ellen Nakashima, Yasmeen Abutaleb, and Joel Achenbach, "Biden Receives Inconclusive Intelligence Report on Covid Origins," *Washington Post*, August 24, 2021.

¹⁶² See Jiumeng Sun et al., "Covid-19: Epidemiology, Evolution, and Cross-Disciplinary Perspectives," *Trends in Molecular Medicine* 26, no. 5 (2020): 484; Di Wu et al., "The Sars-Cov-2 Outbreak: What We Know," *International Journal of Infectious Diseases* 94 (2020).

¹⁶³ See Sun et al., "Covid-19 Epidemiology."

It was quickly determined that the cause of the disease was a coronavirus -- a class of viruses that often causes intestinal and respiratory disorders in both animals and humans. (The “SARS” outbreak, which killed 8000 people in 26 countries during 2002-2003, was caused by another member of the same class.) The new virus was labelled, “SARS-CoV-2,” and the disease it produces, “COVID-19” (an acronym for “coronavirus disease of 2019”).

The disease is not yet fully understood, but its manifestations are well known: Roughly half of infected people are asymptomatic.¹⁶⁴ When symptoms do appear, they usually resemble those associated with influenza: cough, fever, headache, body aches, and so forth. In a substantial minority of cases, however, the patients experience more severe symptoms: among them, pneumonia, dangerously low oxygen levels in the blood, neurological disorders, and damage to major organs.¹⁶⁵ These are especially common in – but are not limited to – persons with comorbidities, such as obesity, diabetes, heart disease, and compromised immune symptoms. Some of the people with severe symptoms are able to recover, especially if they have access to ventilators, oxygen, hospitals, and high-quality care. Others, however, continue to decline and eventually die. Of those who do recover, some experience serious residual symptoms (collectively sometimes called “long Covid”) for months or years.¹⁶⁶

As the threat posed by this disease became increasingly evident, the leaders of a few multilateral institutions – most notably, the G7 and the World Health Organization – attempted to organize a coordinated international response to it. Had those efforts succeeded, the history of COVID-19 might have resembled that of SARS or Ebola. But they did not.¹⁶⁷ Instead, the governments of most nations adopted various unilateral strategies in hopes of halting the spread of the virus into and within their own populations. Most attempted to limit the entry into their territories of infected persons. Some closed their borders altogether or blocked entry from regions with high case loads. Some instituted and enforced mask-wearing or social-distancing requirements. A few adopted rigorous systems for identifying infected persons, tracing everyone with whom they had come into contact, and imposing quarantine requirements on all of them. Many closed schools, restaurants, churches, and workplaces.¹⁶⁸

In general, developed countries initially fared less well than developing countries – in sharp contrast to the pattern that, as we have seen, characterizes most infectious diseases. In particular, in 2020 the United States and the countries in western Europe had the highest case loads and mortality rates. Not all developed countries fared so poorly; for example, Japan,

¹⁶⁴ See Daniel P. Oran and Eric J. Topol, "Prevalence of Asymptomatic Sars-Cov-2 Infection: A Narrative Review," *Annals of Internal Medicine* 173, no. 5 (2020).

¹⁶⁵ See, e.g., Julie Helms et al., "Neurologic Features in Severe Sars-Cov-2 Infection," *New England Journal of Medicine* 382, no. 23 (2020).; Victor G. Puelles et al., "Multiorgan and Renal Tropism of Sars-Cov-2," *ibid.* 383.

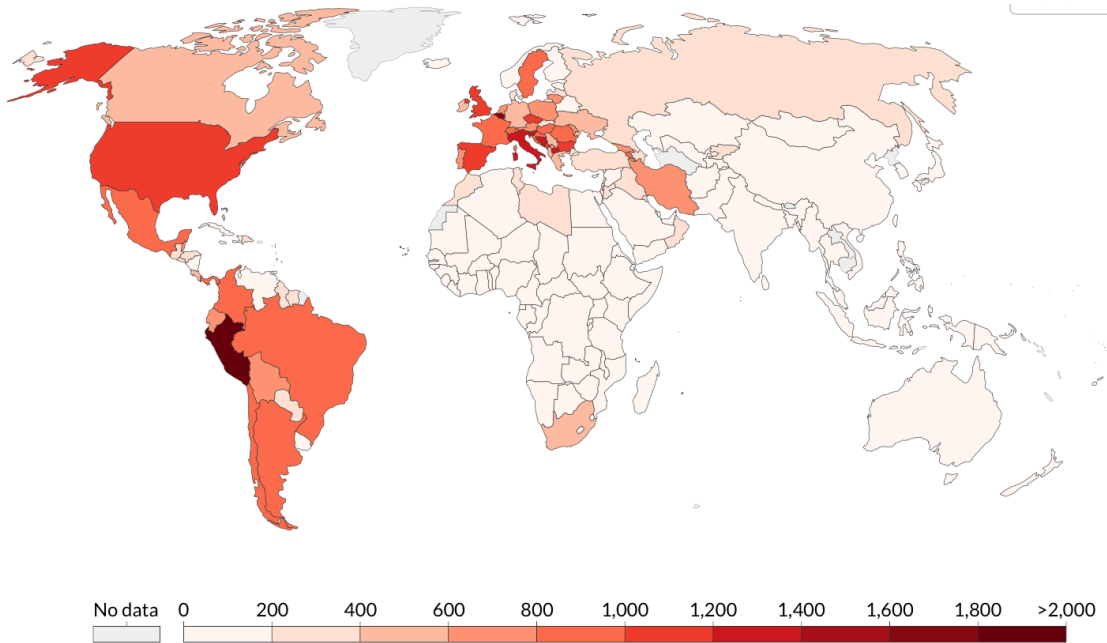
¹⁶⁶ See Bjørn Blomberg et al., "Long Covid in a Prospective Cohort of Home-Isolated Patients," *Nature Medicine* (2021).; Lixue Huang et al., "1-Year Outcomes in Hospital Survivors with Covid-19: A Longitudinal Cohort Study," *Lancet* 398 (2021).

¹⁶⁷ For an effort to explain the failure of these efforts, see Colin Kahl and Thomas Wright, *Aftershocks: Pandemic Politics and the End of the Old International Order* (New York: St. Martin's Press, 2021).

¹⁶⁸ For descriptions and analyses of the strategies adopted by different governments, see Peter Baldwin, *Fighting the First Wave: Why the Coronavirus Was Tackled So Differently across the Globe* (Cambridge University Press, 2021).; Ho Yeung Lam et al., "The Epidemiology of Covid-19 Cases and the Successful Containment Strategy in Hong Kong—January to May 2020," *International Journal of Infectious Diseases* 98 (2020).; Matteo Chinazzi et al., "The Effect of Travel Restrictions on the Spread of the 2019 Novel Coronavirus (Covid-19) Outbreak," *Science* 368 (2020).

Norway, New Zealand, and Australia initially seemed to have dodged most of the bullets. But overall, rich countries suffered. By contrast, in the early stages of the pandemic, most poor countries were largely spared. Again, there were exceptions; for example, Ecuador, Peru, and (to a lesser extent) South Africa were devastated. But in general, developing countries had many fewer cases per capita. This unusual pattern is evident in Figure 12, which shows the cumulative deaths per million people in each country as of December 31, 2020.

Figure 12¹⁶⁹



Source: Johns Hopkins University CSSE COVID-19 Data

In 2021, however, the rich countries began to recover, while the poor countries deteriorated. The cause of the improvement in developed countries was not, as one might have expected, the discovery and distribution of drugs that could cure COVID-19. To be sure, many candidates were tried, but few conferred much benefit.¹⁷⁰ Some, such as hydroxychloroquine, proved useless or worse.¹⁷¹ Remdesivir, an anti-viral drug produced by Gilead, initially seemed capable at least of shortening the duration of patients' hospital stays, but even that benefit proved elusive, and eventually the WHO withdrew its endorsement of

¹⁶⁹ Source: <https://ourworldindata.org/covid-deaths>.

¹⁷⁰ See Haiou Li et al., "Updated Approaches against Sars-Cov-2," *Antimicrobial Agents and Chemotherapy* 64, no. 6 (2020); Dwight L. McKee et al., "Candidate Drugs against Sars-Cov-2 and Covid-19," *Pharmacological Research* 157 (2020).

¹⁷¹ See, e.g., "FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems" (July 1, 2020), <https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or>

the drug as a COVID treatment.¹⁷² As of this writing, three monoclonal antibodies are showing the most promise as COVID treatments, but their distribution thus far has been too small to make a significant dent in the pandemic.¹⁷³

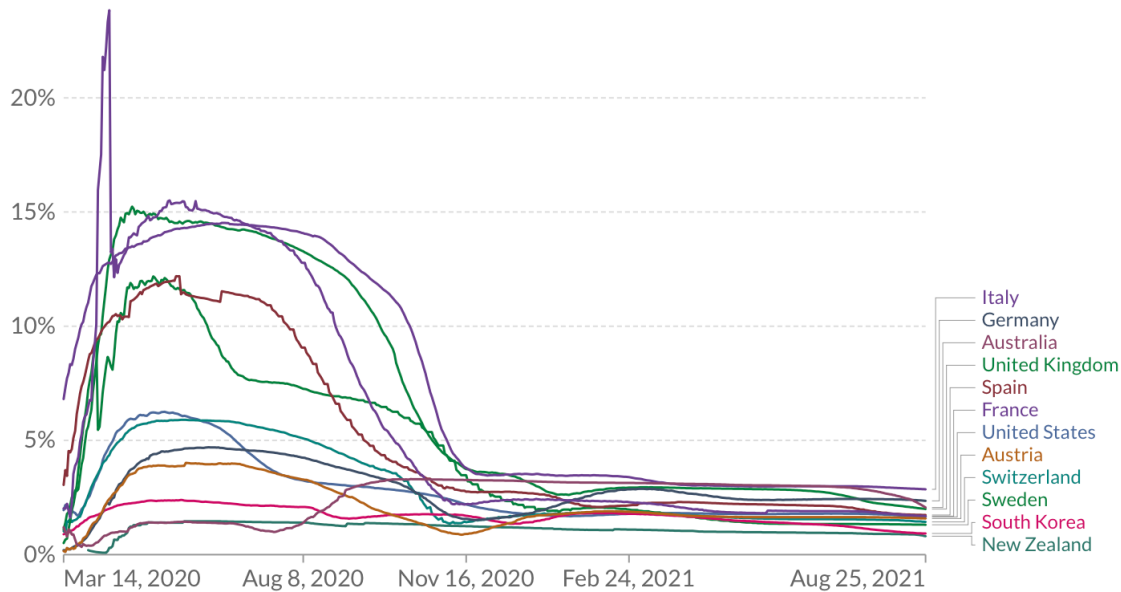
Instead, three factors enabled most developed countries to begin to curb the epidemic. First, as more information about the disease came to light, public-health initiatives designed to impede transmission of the virus slowly became more efficient. Second, health-care workers developed and applied more effective techniques for keeping infected people alive until their bodies could repel the virus.¹⁷⁴ As a result, the case fatality rates in most developed countries plummeted:

¹⁷² For the tangled history of remdesivir, including the efforts, ultimately pointless, to increase its availability in developing countries, see John H. Beigel et al., "Remdesivir for the Treatment of Covid-19 — Final Report," *New England Journal of Medicine* 383, no. 19 (2020).; "Gilead prices remdesivir at \$2,340 per patient for developed countries" *European Pharmaceutical Review* (June 30, 2020); <https://www.europeanpharmaceuticalreview.com/news/122592/gilead-prices-remdesivir-at-2340-per-patient-for-developed-countries/>; Ellen t' Hoen, "Remdesivir developed country price announced," *Medicines Law and Policy* (June 30, 2020), <https://medicineslawandpolicy.org/2020/06/remdesivir-developed-country-price-announced/>; JV Chamary, "The Strange Story Of Remdesivir, A Covid Drug That Doesn't Work" (*Forbes* (January 31, 2021).; "Gilead, "Voluntary Licensing Agreements for Remdesivir," <https://www.gilead.com/purpose/advancing-global-health/covid-19/voluntary-licensing-agreements-for-remdesivir>.

¹⁷³ See "COVID-19 Treatments and Therapeutics," <https://www.hhs.gov/coronavirus/covid-19-treatments-therapeutics/index.html> (last visited August 25, 2021).; NIH, "Anti-SARS-CoV-2 Monoclonal Antibodies," <https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/>; Harvard Medical School, "Treatments for Covid-19," (2021), <https://www.health.harvard.edu/diseases-and-conditions/treatments-for-covid-19>; Kevin Weintraub, "After Slow Start, Demand for COVID monoclonal Antibodies Treatment Skyrockets," *USA Today* (August 25, 2021), <https://www.usatoday.com/story/news/health/2021/08/25/monoclonal-antibodies-treatment-demand-skyrockets-covid-cases-climb/5579505001/>

¹⁷⁴ See, e.g., Eric K. Wei, Theodore Long, and Mitchell H. Katz, "Nine Lessons Learned from the Covid-19 Pandemic for Improving Hospital Care and Health Care Delivery," *JAMA Internal Medicine* (2021), <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2782429>; Donna Marbury, "3 Ways to Improve Healthcare Tech for Better Covid-19 Care," *HealthTech* (2020), <https://healthtechmagazine.net/article/2020/11/3-ways-improve-healthcare-tech-better-covid-19-care>; Ann Kavannah et al., "Improving Health Care for Disabled People in Covid-19 and Beyond: Lessons from Australia and England," *Disability and Health Journal* 14 (2021); National Institutes of Health, "Coronavirus Disease 2019 (Covid-19) Treatment Guidelines," (2021), <https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf>.

Figure 13: Case Fatality Rate in Representative Developed Countries:
March 2020 to August 2021¹⁷⁵



Source: Johns Hopkins University CSSE COVID-19 Data

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Last but not least, a huge investment of money and human resources resulted in the remarkably rapid development of several effective vaccines, large quantities of which were purchased by the governments of developed countries and made available to their residents.¹⁷⁶

Unfortunately, the benefit that developing countries could reap from these three factors was limited. With respect to the first factor, several conditions common in those countries made it difficult to adopt or sustain public-health initiatives: houses are often close together (especially in the poor sectors of urban areas); most residents have neither savings nor credit and thus must go to work to survive; meager Internet access limits opportunities to work at home; lack of refrigeration necessitates daily shopping; and limited sanitation inhibits the adoption of protective measures.¹⁷⁷ With respect to the second, most developing countries lacked enough hospital beds and health-care workers to provide infected persons the kind of care that was increasingly available in high-income countries. With respect to the third, the bulk of the first wave of effective vaccines were purchased (typically well in advance of their

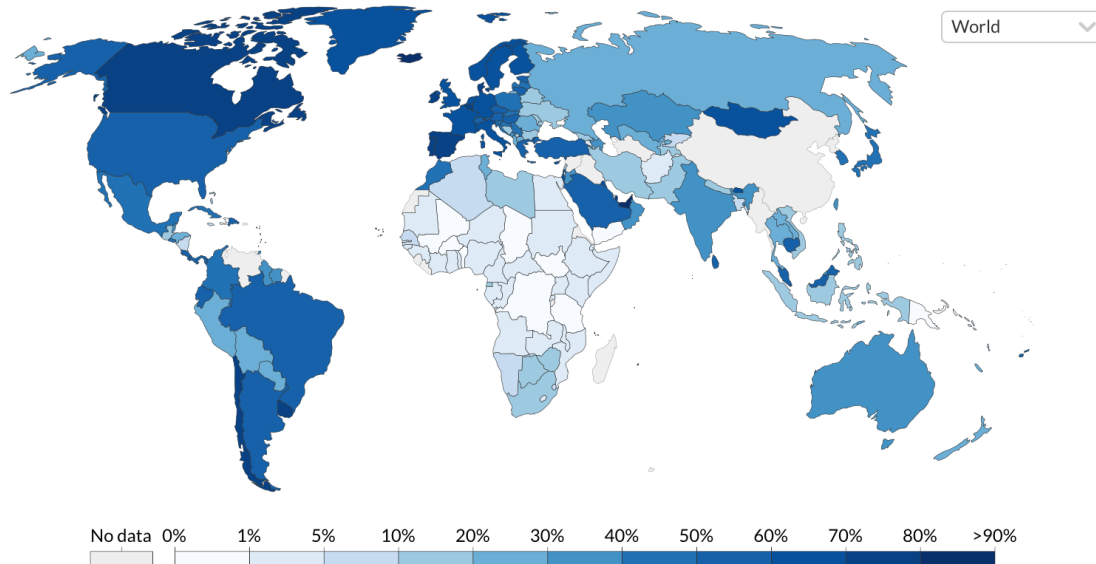
¹⁷⁵ Source: <https://ourworldindata.org/mortality-risk-covid>.

¹⁷⁶ As of this writing, seven COVID vaccines are included in the WHO's emergency use listing, and 19 have been approved by at least one national authority. See UNICEF, "Covid-19 Vaccine Dashboard," <https://www.unicef.org/supply/covid-19-vaccine-market-dashboard> (last accessed 30 June 2021). The remarkable story of the rapid development of these vaccines can be traced in Florian Krammer, "Sars-Cov-2 Vaccines in Development," *Nature* 586 (2020); L.A. Jackson et al., "An Mrna Vaccine against Sars-Cov-2 — Preliminary Report," *New England Journal of Medicine* 383, no. 20 (2020); L.R. Baden et al., "Efficacy and Safety of the Mrna-1273 Sars-Cov-2 Vaccine," *ibid.* 384, no. 5 (2021). The funding strategies that made this possible are described in Chapter 2, Section A.1, below.

¹⁷⁷ See Matthew E Levison, "Covid-19 Challenges in Developing Countries," *Merck Manual* (2020); Terrence McCoy and Heloisa Traiano, "Brazil's Densely Packed Favelas Brace for Coronavirus: 'It Will Kill a Lot of People.'," *Washington Post*, March 21, 2020; Yasmeen Serhan, "Where the Pandemic Is Only Getting Worse," *The Atlantic* (2020); Brett Walton, "Healthcare Facilities in Developing Countries a High Risk for Coronavirus Transmission," *New Security Beat* (2020).

manufacture) by developed countries, leaving little for the developing world.¹⁷⁸ As of this writing, the supply of vaccines to developing countries is at last gradually increasing, in part because of efforts by the COVID-19 Vaccines Global Access Facility (“COVAX”) to secure vaccine batches on their behalf and in part because of modest donations by developed countries of doses that they find they do not need. But the flow remains insufficient to meet demand. As one might expect, the net result (evident in figure 13) has been radical disparity among countries in the administration of vaccines.

Figure 13: Share of the Population that has Received at Least One COVID-19 Vaccine Dose, August 14, 2021¹⁷⁹



Source: Official data collated by Our World in Data – Last updated 15 August 2021, 10:20 (London time) [OurWorldInData.org/coronavirus](https://ourworldindata.org/coronavirus) • CC BY
 Note: This data is only available for countries which report the breakdown of doses administered by first and second doses.

The fruit of this combination of factors: most countries in Latin America are now suffering at least as badly as those in North America and Europe, and variants of the virus are spreading rapidly in Africa, India, and Indonesia.¹⁸⁰ A short video, showing the erratic but seemingly inexorable shift in the concentration of COVID deaths from the developed to the developing world is available at [insert COVID_Deaths.mp4].

¹⁷⁸ See Megan Twohey, Keith Collins, and Katie Thomas, "With First Dibs on Vaccines, Rich Countries Have ‘Cleared the Shelves’," *New York Times*; Padmeshree Gehl Sampath, "Covid-19 and the Need for a New Global Health Diplomacy," *Harvard Public Health Review*, 2021 (29), available at: https://harvardpublichealthreview.org/29-article-gehlsampath/#_ftn1

¹⁷⁹ Source: <https://ourworldindata.org/covid-vaccinations>. Note, in particular, the dire situation in Africa. In the United States, despite the resistance of many people to being vaccinated, over 60% of the population has already received at least one dose; in Africa, the number currently is under 2%. Ibid.

¹⁸⁰ See, e.g., Johns Hopkins Coronavirus Resource Center, "Mortality in the Most Affected Countries," <https://coronavirus.jhu.edu/data/mortality> (showing that, as of August 22, 2021, total deaths per 100,000 population in Peru, Brazil, Colombia, Argentina, and Mexico exceed the number in the United States); Richard C. Paddock and Mukti Suhartono, "No Longer ‘Hidden Victims,’ Children Are Dying as Virus Surges in Indonesia," *New York Times*, July 31, 2021.; Jinshan Hong, Randy Thanthong-Knight, and Jason Scott, "It’s Not Just India: New Virus Waves Hit Developing Countries," *Bloomberg* (2021).

The proliferation of variants of the virus and ongoing struggles over vaccination practices and public-health initiatives makes it difficult to predict how the pandemic will progress in each nation. But there is little doubt that, for the foreseeable future, developed countries will continue to have disproportionate access to the tools necessary to combat the virus. As a result, both infections and deaths will soon be concentrated in the developing world¹⁸¹ -- just as they are with respect to tuberculosis, malaria, HIV, dengue, and Ebola.

¹⁸¹ See Indermit Gill and Philip Schellekens, "Covid-19 Is a Developing Country Pandemic," *Brookings* (2021), <https://www.brookings.edu/blog/future-development/2021/05/27/covid-19-is-a-developing-country-pandemic/>; United Nations, "As Developed Nations Spring Back to Life, the World's Most Vulnerable Struggle on the Sideline," (2021), <https://www.un.org/ohrlls/news/developed-nations-spring-back-life-worlds-most-vulnerable-struggle-sideline>.

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