Chapter 1: Diseases

This chapter summarizes the epidemiology of five of the infectious diseases that currently afflict the developing world. Three of the five were chosen because of the scale of the harm they cause; HIV/AIDS, tuberculosis, and malaria each result in the loss of between 35 and 60 million DALYs per year. The burdens associated with Ebola are much lower, but the threat that it and its cousins pose to developing countries is enormous. Finally, 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.

Most aspects of the history and current status of these five diseases are grim, 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 five 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 these five should suffice to launch our inquiry.

A. HIV/AIDS

Viruses are the smallest infectious agents. Lacking cell structure themselves, they survive and reproduce by invading the cells of other organisms. An especially dangerous member of this group is the human immunodeficiency virus (HIV), the principal manifestation of which is Acquired Immune Deficiency Syndrome (AIDS).

Today, roughly 38 million people in the world are infected with HIV.[1] Each year, roughly 750,000 of them die. This is significantly fewer than the 2.4 million who died during 2005, the peak year of the epidemic, but still an appalling number. Since 2001, the number of people who are newly infected with HIV each year has been declining, but it is still 1.7 million.[2] The result is that the total number of people living with HIV in the world continues to climb.

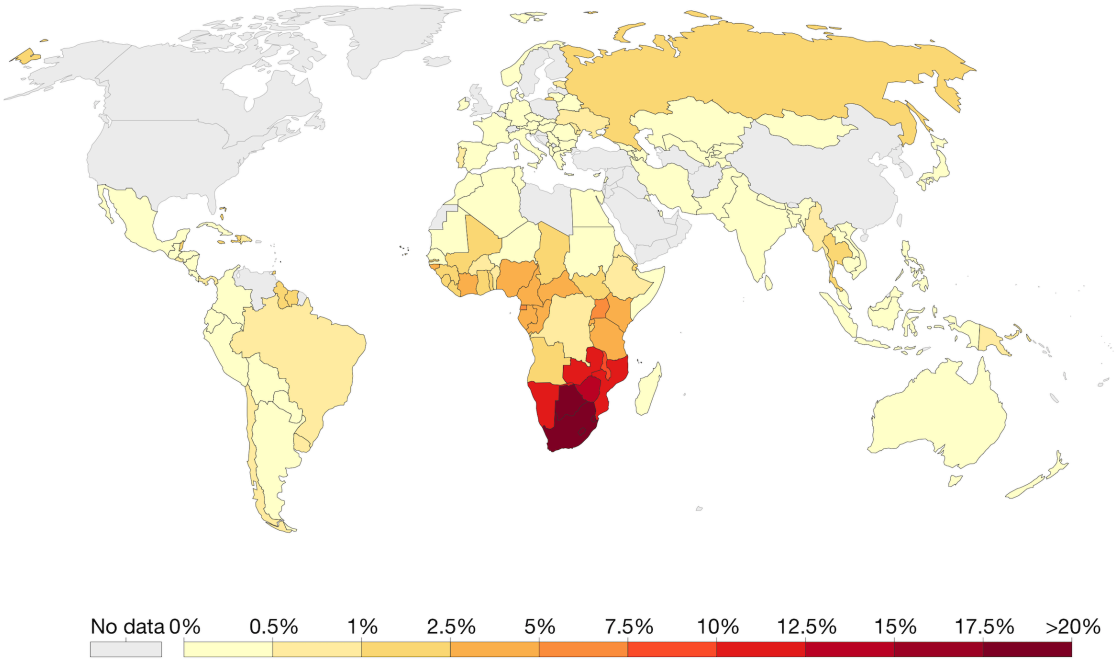
The adult prevalence of the disease (as of 2017) is shown in the following map.[3]

[1] World Health Organization, *HIV/AIDS, Data and Statistics*, http://www.who.int/hiv/en/.

[2] Source: UNAIDS, "Global Hiv & Aids Statistics — 2019 Fact Sheet," (2019), https://www.unaids.org/en/resources/fact-sheet.

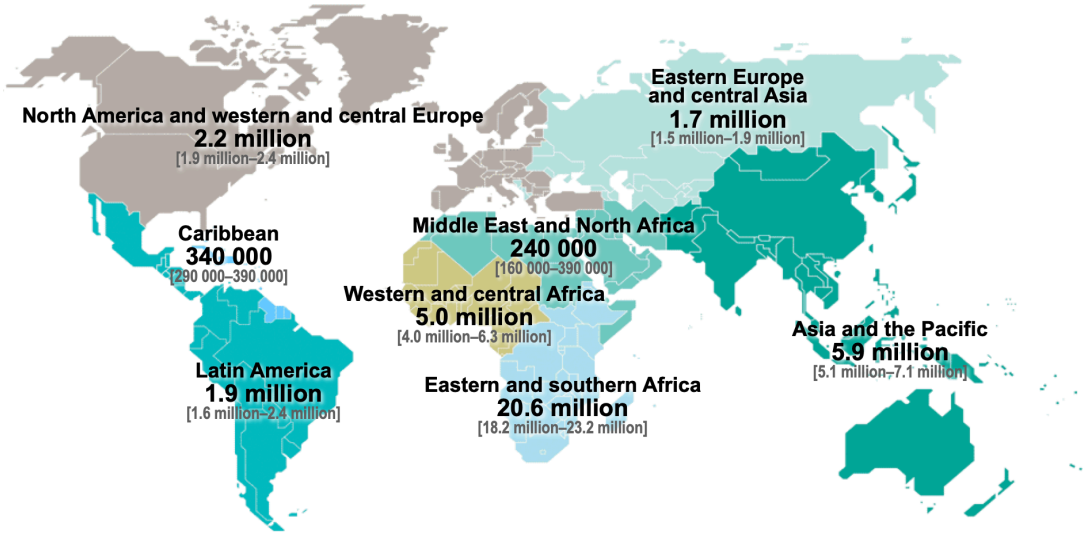
[3] Source: https://ourworldindata.org/hiv-aids.

Figure 1: Prevalence of HIV (2017)
(Share of the population between 15 and 49 years old infected with HIV)[4]



As the following figure shows, the large majority of the infected people live in subSaharan Africa or southeast Asia.[5]

Figure 2: Adults and children estimated to be living with HIV | 2018



[4] This figure was created by Our World in Data, using numbers provided by UNAIDS. The original is available at https://ourworldindata.org/hiv-aids.

[5] Source: UNAIDS.

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 its 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.

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, Karposi's sarcoma, disorders of the central nervous system).[6]

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

[6] 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).

transcriptase inhibitors, which impede the process, described above, by which modified DNA is generated from HIV RNA. Inhibitors of this sort include zidovudine (AZT), tenofovir (TDF), lamivudine (3TC), staduvine (d4T), and emtricitabine (FTC).[7] Combinations ("cocktails") of these drugs have proven to be more effective that single drugs; typically, they are administered in combinations of three.[8]

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. PIs that target HIV include saquinavir (developed by Roche), ritonavir (developed by Abbott [renamed AbbVie]), indinavir (developed by Merck), nelfinavir (developed by Agouron Pharmaceiuticals and Eli Lilly), and fosamprenavir (a variant of amprenavir, developed by GlaxoSmithKline). If the second-line drugs lose effectiveness, they are replaced by "third-line" ARVs – sometimes called "salvage regimens."[9]

Of the infectious diseases that afflict developing countries, HIV has received by far the most attention from researchers, foundations, pharmaceutical firms, and governments. 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;[10] the genetic diversity among HIV strains and the speed with which the virus evolves in vivo;[11] and the difficulty of inducing immune protection in the mucosa, where the virus commonly enters the body.[12]

Despite these impediments, progress in the development of a vaccine is at last being made. HVTN 702 (Uhambo), which targets the strain most common in subSaharan Africa, is currently being tested on 5,400 adults in South Africa, and HVTN 705 (Imbokodo), a broad-

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[7] 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.

[8] 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).

[9] See, e.g., Khan et al., Second-line Failure and First Experience with Third-Line Antiretroiviral 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.

[10] *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.

[11] 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.

[12] WHO, "Global Update on the Health Sector Response to Hiv, 2014," (2014)., p. 23.

spectrum candidate, is being tested on 2,600 women in five African countries. Even if (as is likely) neither proves to be the Holy Grail, chances are good that one of the several additional candidates currently in the pipeline will prove efficacious.[13]

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);[14]
- male circumcision (which significantly reduces sexual transmissions from females to males, though not necessarily transmissions from males to females or males to males);[15]
- 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;[16]
- providing sterile or disposable syringes to intravenous drug users;[17]
- prophylactic administration of ARVs, especially to the infected partners in serodiscordant couples[18] and to infected pregnant women (which, if begun early enough, nearly eliminates transmission of the virus to their children);[19]
- testing blood supplies, to prevent transmission through infusions;[20] and

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[13] See AIDS Vaccine Advocacy Coalition, "Hiv Vaccines: An Introductory Factsheet," (2019). For earlier, less optimistic discussions of efforts to generate a vaccine that would either slow the progress of the disease or prevent it altogether, see 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). Some reasons for pessimism about this approach are presented in 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); WHO, "Global Update on the Health Sector Response to Hiv, 2014.", p. 23.

[14] 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 "Global Update on the Health Sector Response to Hiv, 2014.", pp. 11-12.

[15] 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).

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

[17] 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/effectivenessstrileneedle.pdf?ua=1; WHO, "Best Practices for Injections and Related Procedures ToolKit" (2010), http://www.who.int/injection_safety/toolbox/9789241599252/en/.

[18] WHO, Note 51

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

[20] 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;[21] the government of Brazil used its bargaining power to extract major price concessions from some of the pharmaceutical firms;[22] 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.[23] 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.[24] The percentage of HIV-positive people throughout the world who now receive ART is roughly 62% (up from 10% in 2006) and rising.[25]

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

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[21] See AVERT, "Antiretroviral Drug Prices," http://www.avert.org/antiretroviral-drug-prices.htm.

[22] 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).

[23] See MSF, *Untangling the Web of Antiretroviral Price Reductions — 18th Ed.*; 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.

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

[25] See UNAIDS, "Global Hiv & Aids Statistics — 2019 Fact Sheet".; Initiative, "Hiv Market Report."

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, 38% 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 remain expensive, especially in middle-income countries.[26] 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.

B. Tuberculosis

Tuberculosis (TB), unlike HIV, is caused by bacteria. Today, the overwhelming majority of TB cases result from one species, *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);[27] *mycobacterium caneti* (confined to the Horn of Africa); and *mycobacterium microti* (which sometimes occurs in HIV-positive persons).

The primary way in which the TB bacteria are transmitted is through the inhalation of water droplets suspended in air that has been contaminated by a cough or sneeze from someone with an active TB infection.[28] A few of those droplets reach the alveoli in the person's lungs, where the bacilli multiply; eventually, they spread to the lymph nodes and onward to other organs in the body.[29] An immune response usually kills off most of the bacilli, leaving behind granulomas (clusters of immune cells) in the tissue.[30] At this point, the person is said to be "infected," but is asymptomatic.

The large majority of tuberculosis 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.[31] 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

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[26] See MSF, *Untangling the Web of Antiretroviral Price Reductions — 18th Ed.* 7-10.; Initiative, "Hiv Market Report."

[27] 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).

[28] *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.*

[29] *See id.* at 7.

[30] See id.

[31] See id.

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.[32]

The main treatment for active TB is a course of antibiotics.[33] The drugs most commonly used are rifampicin and isoniazid. They are now often combined with two more: ethambutol and pyrazinamide.[34] 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.[35] Their lapses accelerate the development of drug-resistant strains of the bacteria in their bodies, which not only reduces their own responsiveness to antibiotics, but heightens the hazard that they pose to others. The "Directly Observed Therapy Short-course" (DOTS) (developed by the WHO[36]), in which a health-care worker monitors each patient's consumption of the antibiotics,[37] is intended (among other things) to minimize such lapses, but its effectiveness in this particular respect is doubtful.[38]

Several varieties of drug-resistant resistant strains have now been identified.[39] "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.[40] "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.[41] Roughly 3.4% of all

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[32] 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).

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

[34] 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.

[35] *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).

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

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

[38] 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.

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

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

[41] 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

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.[42]

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

A vaccine for TB does exist. Commonly known as BCG (after its developers, Albert Calmette and Camille Guérin), it is based on a strain of *Mycobacterium bovis* that was attenuated a century ago.[43] It is currently administered to approximately 100 million persons a year.[44] BCG has proven to be highly effective in preventing TB infection during childhood.[45] Unfortunately, it is much less effective in preventing pulmonary TB in adults.[46] A number of hypotheses have been suggested to explain this phenomenon. Some scientists contend that the protection induced by BCG wanes over time.[47] Others believe that variation in the strains of the TB virus accounts for the differences in protection afforded by the vaccine.[48] 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.[49] Whatever the reason, BCG provides adults little protection against the disease.

Unlike HIV, which first passed from non-human primates to humans sometime in the twentieth century, TB has afflicted humans for thousands of years. By 1800, it was extremely common, especially among the urban poor. During the nineteenth century, roughly one quarter of all deaths in Europe resulted from TB.[50] Public-health initiatives designed to reduce transmission rates, combined with the increasingly widespread deployment of the BCG vaccine and antibiotics, sharply reduced both its prevalence and its mortality rate – and gave rise to hope that, like smallpox, TB might be eradicated altogether. Optimism on this score

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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.

[42] 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.

[43] 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).

[44] *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.

[45] 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).

[46] *See supra* Brennan at 7.

[47] *See supra* Doherty at 818.

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

[49] *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.*

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

has now dissipated, in part because of the emergence of the drug-resistant strains and in part because of the spread of the HIV virus, which (as indicated above) has increased the frequency with which latent TB infections become active and thus contagious.

Today, between one quarter and one third of the world's population is infected with one of the tuberculosis viruses.[51] Roughly 10 million people develop the active form of disease each year, and 1.45 million die from it.[52] 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.[53] Figures 3 and 4, below, show the geographic distribution, as of 2018, of new TB infections and of TB mortality rates (excluding the deaths related to HIV).[54]

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

[52]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.

[53] See WHO, *2019 Global Tb Report*, 27.

[54] The figures are derived from ibid., 38, 47.

Figure 3: Estimated TB Incidence Rates, 2018

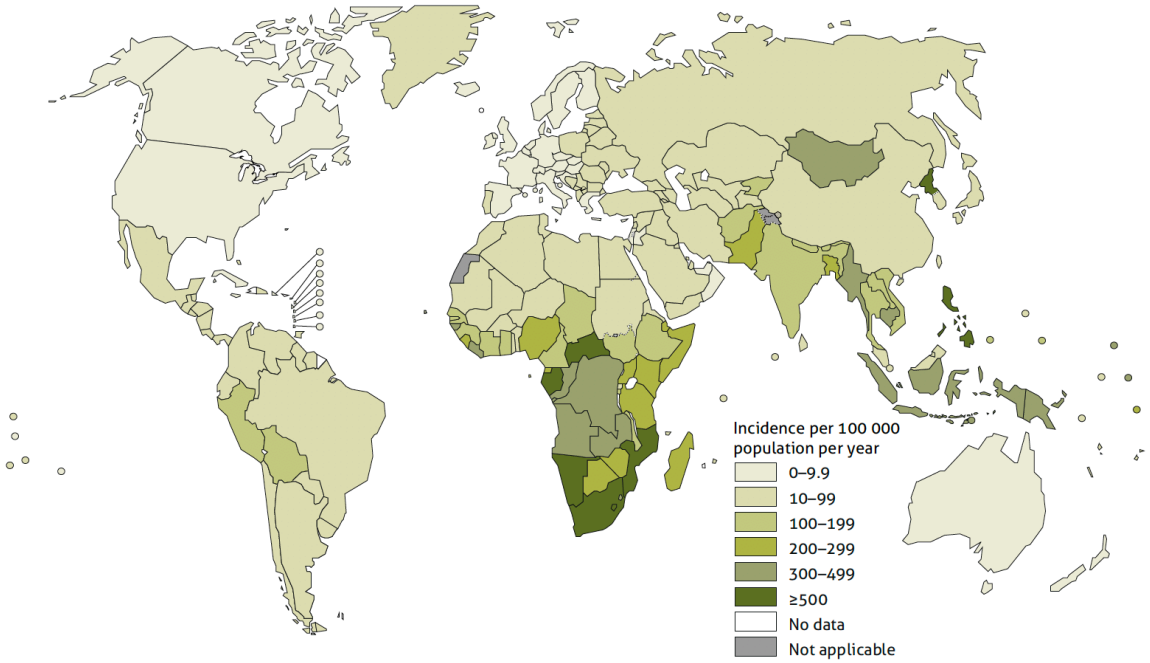
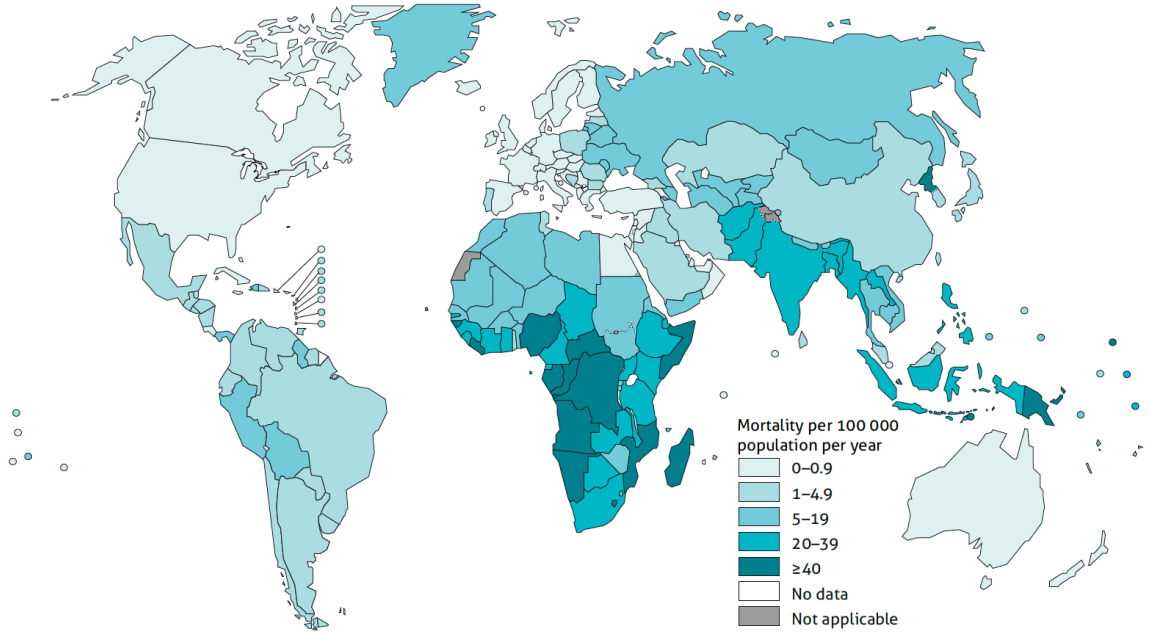


Figure 4: Estimated TB Mortality Rates, 2018
(excluding TB Deaths among HIV-positive people)



The high levels both of new infections and of deaths in subSaharan Africa evident in these maps resemble the level of HIV in that region. In other respects, however, the geographic distribution of TB is different from that of HIV. In particular, TB currently

threatens even more severely than HIV the population of Asia. (In 2018, 27% of all new TB cases were in India, 9% were in China, and 8% were in Indonesia.[55])

If successful, two lines of research would go far to curbing the scourge of TB. First, efforts are currently underway to develop new antibiotics capable of combatting the drug-resistant forms of the disease.[56] Two (bedaquiline and delamanid) have recently been approved; ten more are being tested.[57] Second, various projects are seeking to develop a vaccine that would either be more effective than BCG[58] or would boost the effectiveness of BCG in adults.[59] 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.[60] Many pharmaceutical companies and research centers are participating.[61] 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.[62] And, although some of the vaccine candidates have been shown to be safe, none has yet been demonstrated to be effective.[63]

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

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[55] See ibid., 27, 35.

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

[57] 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).

[58] 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.

[59] 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.*

[60] *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).

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

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

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

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.[64] Even the clinical trials for booster vaccines typically span 8-10 years.[65] A limited clinical-testing and manufacturing infrastructure also contributes to slow development of viable TB vaccines.[66] Working with the live pathogens used in attenuated *M.tuberculosis* or recombinant BCG vaccines requires biohazard-level-3 facilities.[67] 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.[68]

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.[69] 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$100 and US$500 in most countries, the average cost per patient of treating MDR-TB is roughly US$6430 (18% of which consists of the costs of the second-line drugs; the balance of the costs of care).[70] 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:

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[64] *See supra* Doherty at 824.

[65] See id.

[66] *See supra* Brennan at 11.

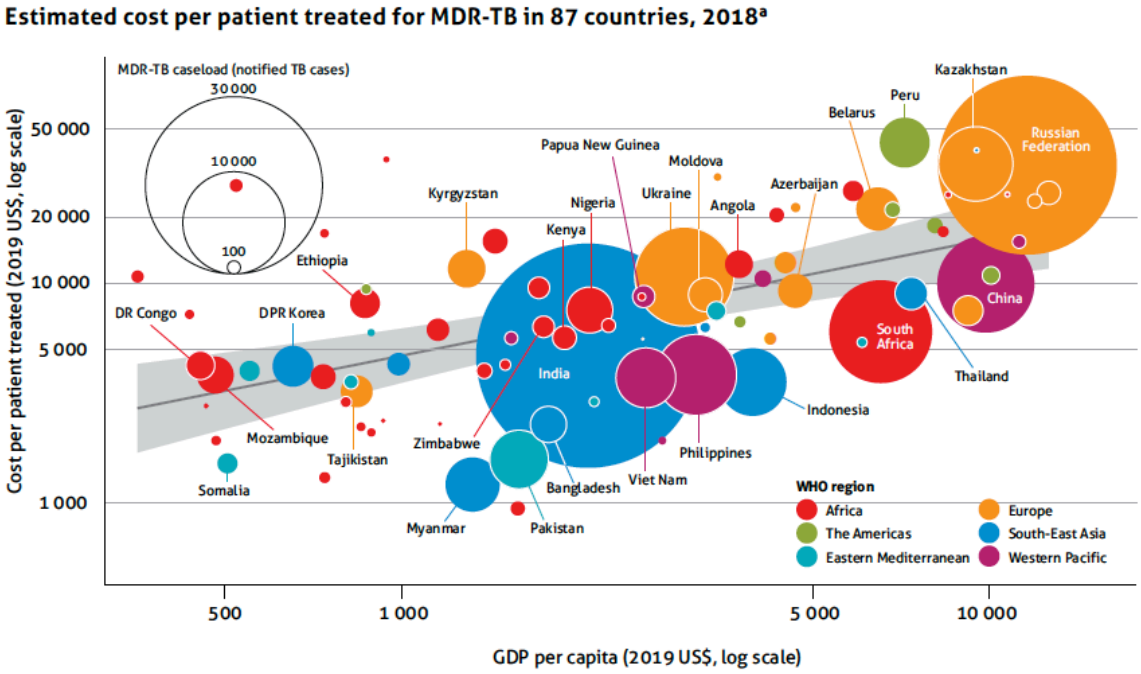
[67] *See id.* at 8.

[68] See id.

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

[70] See 2019 report, 137

Figure 5[71]



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.[72]

Meanwhile, new varieties of drug-resistant TB continue to proliferate, and the threat they pose to public health intensifies.[73] In 2018, there were roughly half a million new cases of MDR-TB, and 214,000 people died from it.[74] 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 (especially Russia and in eastern Europe[75]) and the apparent proliferation of varieties that are resistant to *all* drugs are causes for alarm.

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[71] 2019 Report, 138.

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

[73] 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.

[74] See 2019 TB Report, 58.

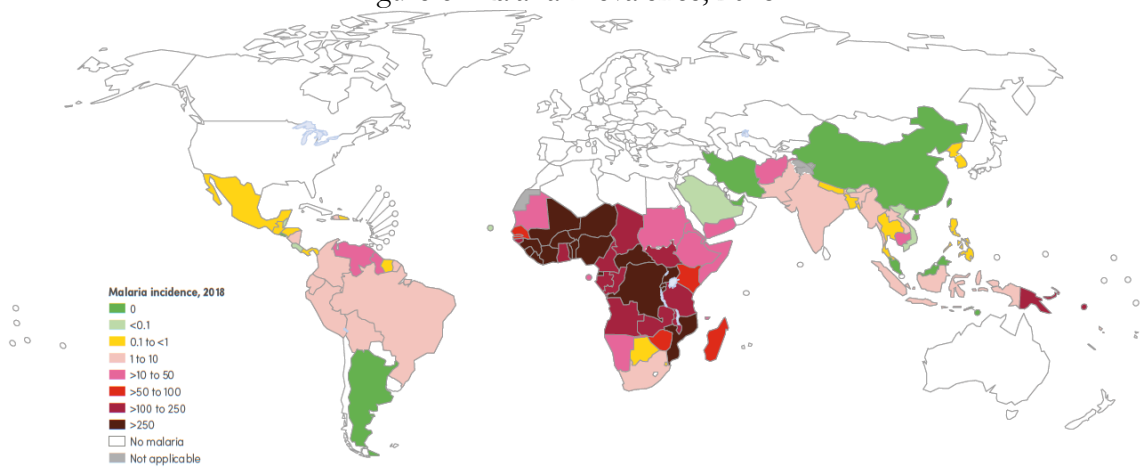
[75] In Russia, 19% of new TB cases and 49% of retreatment cases are drug resistant. In Belarus, the numbers are 35% and 55%; in Kyrgyzstan, 26% and 55%. See WHO, "Global Tb Report," 73.

C. Malaria

Malaria infection in humans originates from the bite of a female Anopheles mosquito carrying the sporozoite form of a *Plasmodium* parasite in her salivary gland.[76] 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.[77] Temporarily safe from the host's immune response, the sporozoites multiply rapidly to form schizonts, each containing merozoites (a second form of the parasite).[78] The schizonts then rupture, spilling thousands of merozoites into the bloodstream where they invade red blood cells and multiply until the host cells burst.[79] 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."[80]

Because transmission of the disease occurs only through bites from specific species of mosquitos (all within the Anopheles family), malaria is common only in countries where those mosquitos flourish, all of which are near the Equator. The geographic distribution of the disease is shown in Figure 6, below.

Figure 6: Malaria Prevalence, 2018[81]



Five species of the Plasmodium parasite are responsible for malaria in humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium*

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[76] *See* Gina Kolata, *The Search for a Malaria Vaccine*. 226 SCIENCE 679, 680 (November 9, 1984).

[77] *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 believe that the sporozoites migrate through host cells. *See id.* at 1114.

[78] *See supra* Kolata at 680.

[79] See id.

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

[81] Source: WHO, "World Malaria Report," (2019), 8.

knowlesi.[82] The most lethal of the five, *P. falciparum*, is the dominant species in Africa.[83] *P. vivax* accounts for roughly half of the cases in Latin American and Southeast Asia,[84] but does little harm in Africa.[85]

As yet, there is only one approved vaccine for malaria, and its effectiveness is marginal. In clinical trials, RTS,S/AS01 (developed by GlaxoSmithKline with support from the Malaria Vaccine Initiative) demonstrated a 46% reduction in clinical malaria incidence in children; 27% in infants.[86] This year (2019), pilot projects to assess the benefits of the vaccine in the field have been launched in Malawi, Ghana, and Kenya, but no one expects that they will show more than moderate benefit.[87] Several other research projects are underway, but none is close to developing an effective vaccine.[88]

In the absence of a vaccine, inhibition of the spread of the disease is achieved 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.[89] They are inexpensive to produce, and their effect is dramatic. Studies suggest that they reduce malaria incidence by half.[90] 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.[91]

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

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

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

[85] "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.

[86] See 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).

[87] See 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.

[88] See "Mvi Portfolio," (2019), https://www.malariavaccine.org/projects/mvi-portfolio.

[89] See WHO, "2019 Malaria Report," xvi, 28-29, 46-48.

[90] 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).

[91] See WHO, "2019 Malaria Report," xvi, 48-49.

Unfortunately, both of these approaches are threatened by increases in the resistance of the pertinent species of mosquitos to the most commonly used insecticides.[92] 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.[93]

Persons who, despite these efforts at vector control, acquire malaria can and should be treated with drugs. In the early twentieth century, the drug used most often was chloroquine. 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).[94] Resistance to SP emerged soon thereafter.[95]Today, most health services outside of Latin America use artemisinin-based combination therapy (ACT) as the primary means of treatment.[96] Artemisinins are remarkably effective. For example, they have been shown to reduce infant mortality caused by malaria by 99%.[97]

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.[98] 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.[99] This has had two bad effects. First, the drugs do those

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

[93] See WHO, "Malaria Report 2014," 16-17.

[94] 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.

[95] See Bell and Winstanley, "Treatment of Malaria in Africa," 31.

[96] *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.

[97] See ibid., 4. The effects on mortality and morbidity of the cycles of drugs and resistance thereto – and the large gains achieved through the swtich 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).

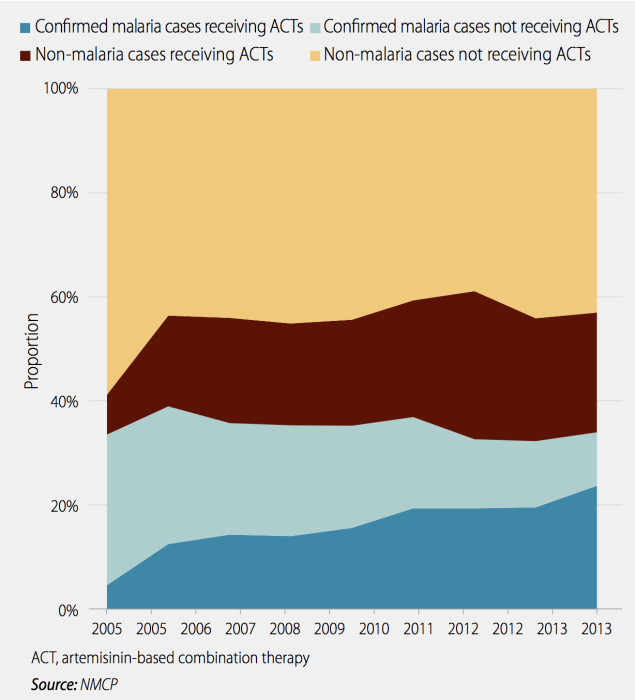
[98] See WHO, "2019 Malaria Report," 59.

[99] 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 not.

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.[100] But, despite this 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.[101])

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.[102] 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.[103]

In the early twentieth century, the vector-control programs and the increasingly widespread distribution of ACT drugs, in combination, substantially reduced both the



See "Malaria Report 2014," 27.

[100] See Bell and Winstanley, "Treatment of Malaria in Africa," 32.

[101] See WHO, "Malaria Report 2014," 28.

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

[103] See "2019 Malaria Report," 14, 21-22.

incidence and the mortality of malaria. In recent years, however, progress has slowed. The global incidence rate dropped from 72 (per 100,000 people) in 2010 to 61 in 2014, but has held steady since.[104] As the following figure shows, the number of malaria deaths, globally, continues to decline – but at a diminishing pace.

Figure 7: Estimated Number of Malaria Deaths by WHO Region[105]

	Number of deaths								
	2010	2011	2012	2013	2014	2015	2016	2017	2018
African	533 000	493 000	469 000	444 000	428 000	411 000	389 000	383 000	380 000
Americas	459	444	392	391	289	324	474	620	577
Eastern Mediterranean	8 300	7 500	7 600	6 900	6 900	7 100	8 600	9 200	9 300
European	0	0	0	0	0	0	0	0	0
South-East Asia	39 000	32 000	28 000	21 000	24 000	25 000	25 000	20 000	12 000
Western Pacific	3 800	3 300	3 600	4 600	4 400	2 800	3 500	3 600	3 600
World (total)	**585 000**	**536 000**	**508 000**	**477 000**	**463 000**	**446 000**	**427 000**	**416 000**	**405 000**
World (children aged under 5 years)	**450 000**	**406 000**	**377 000**	**348 000**	**334 000**	**311 000**	**290 000**	**278 000**	**272 000**

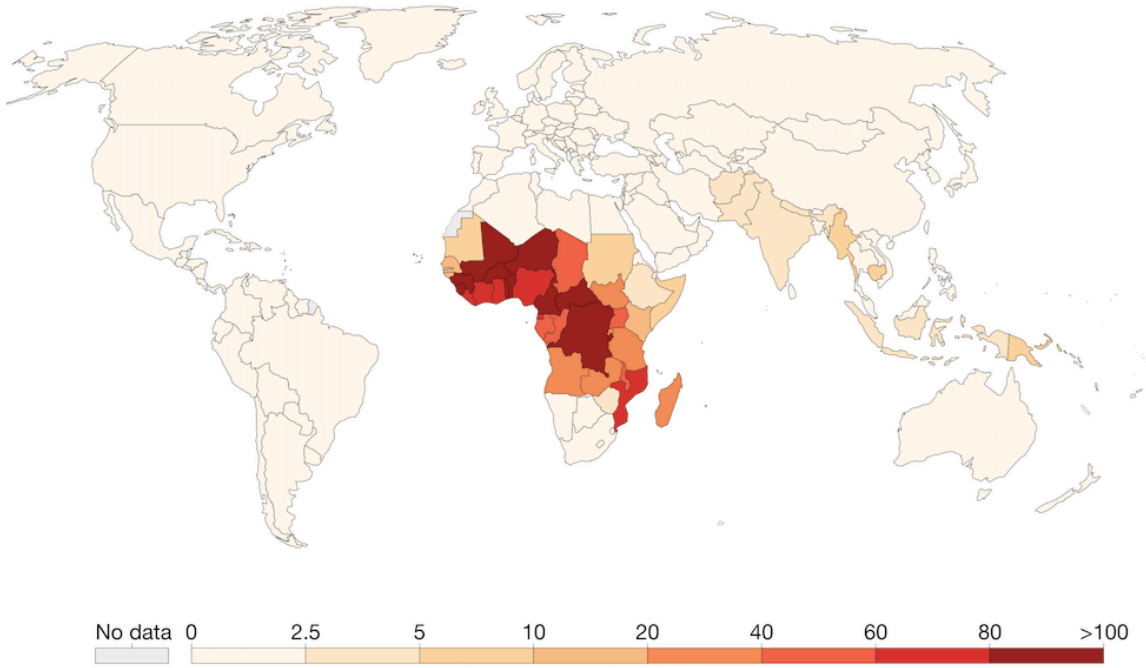
Comparison of the last two lines in this chart reveals that the large majority of the deaths attributable to malaria continue to involve young children.

A more detailed geographic breakdown of mortality rates appears below:

[104] See "World Malaria Report, 2018," (2018): 41.

[105] "2019 Malaria Report," 10.

Figure 8: Age-standardized Malaria Mortality Rate
(per 100,000 population)[106]



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.[107]

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.[108] 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 the national borders in the region and from the residents of the remote forest villages is a daunting task.[109]

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[106] This map has been prepared by Our World in Data, using numbers provided by IMHE, Global Burden of Disease. It is available at https://ourworldindata.org/malaria.

[107] 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).

[108] See WHO, "2019 Malaria Report," 68-71.

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

Once again, therefore, we confront the importance of developing new, more efficacious drugs and, better yet, a vaccine. Unfortunately, the obstacles to the discovery, testing, and deployment of a 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. 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." (GSK's drug, RTS,S, discussed above, pursues the first of these paths, but has had limited success.) 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 nearly impossible. 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.[110]

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.[111] But unless we can meet these challenges, we are unlikely to eradicate the disease.

D. Ebola[112]

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

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[110] 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.

[111] 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 Ojakaa et al., "Acceptance of a Malaria Vaccine by Caregivers of Sick Children in Kenya," *Malaria Journal* 13 (2014).

[112] 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.

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).[113] These symptoms typically first appear 8 to 10 days after exposure to the virus.[114] 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.[115]

Key to the virulence of the virus is its surface glycoprotein, which mediates viral entry into host cells.[116] 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.[117]

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 in 6 other species.[118] 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.[119] Infections are transmitted from one person to another through direct contact with: the blood or body fluids

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

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

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

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

[117] 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).

[118] The three principal species are *Epomops franqueti*, *Hypsignathus monstrosus*, and *Myonycteris torquata*. Insectivorous free-tailed bats (*Mops condylurus*) may also be carriers. See A. Saézet 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.

[119] CDC, "Ebola – Transmission," http://www.cdc.gov/vhf/ebola/transmission/index.html, (last visited June 12, 2015); Saézet al., "Investigating the zoonotic origin."

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.[120] Currently, the only 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 22 documented outbreaks in humans. Details concerning those outbreaks are presented in the following table and accompanying map.[121]

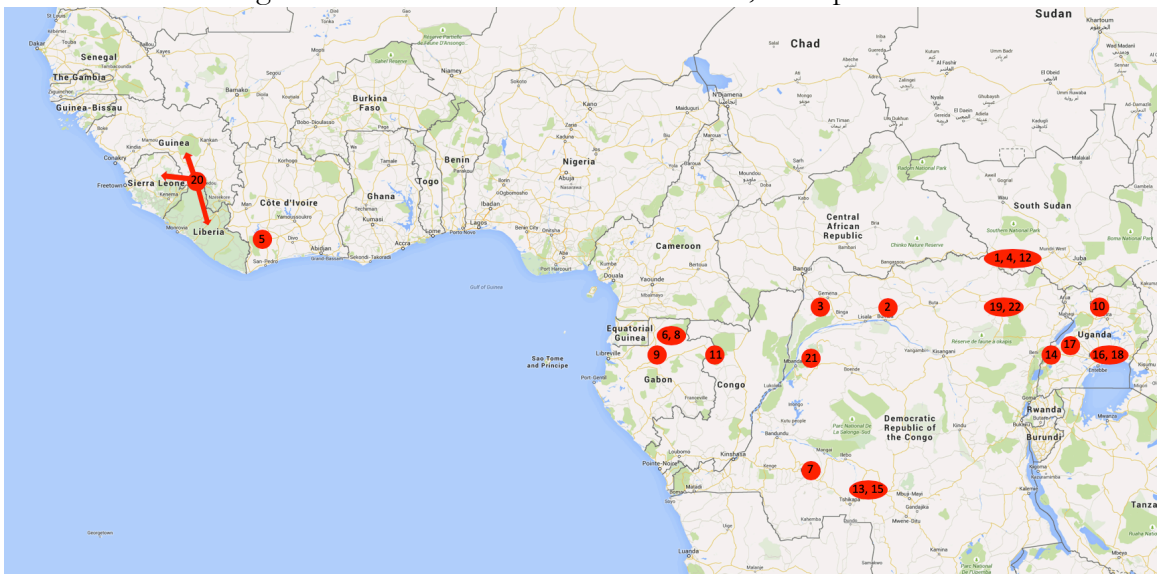
[120] CDC, "Ebola – Transmission"; Gibrilla Deen st al., New England Journal of Medicine, Oct. 14, 2015. There is no evidence that the virus is transmitted through the air or water – or via insects.

[121] 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 October 14, 2015); and WHO, "Ebola in the Democratic Republic of Congo: Health Emergency Update," https://www.who.int/emergencies/diseases/ebola/drc-2019 (last visited, December 7, 2019). 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	Taï National Park, Ivory Coast	1994	Taï 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	Mvoung, 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%

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.[122] 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.[123] 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.[124]

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.[125] 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.[126] 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

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[122] 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).

[123] See Wauquier, "Human Fatal Zaire Ebola Virus Infection."

[124] See Sullivan, "Ebola Virus Pathogenesis."

[125] See N. Stylianou, "How World's Worst Ebola Outbreak Began with One Boy's Death," *BBC News*, 27 November 2014.

[126] BBC, "Ebola: Mapping the outbreak," updated 5 June 2015, available at: http://www.bbc.com/news/world-africa-28755033

home.[127] By the spring of 2015, the virus had infected over 27,000 people and claimed over 11,000 lives.[128]

The most recent outbreak has been concentrated in the Democratic Republic of Congo (formerly Zaire). Although less severe than the West Africa Outbreak, it has been substantial. So far, 3,313 people have been infected, and 2,203 have died. As of August 2019, it appeared that the outbreak had been contained, but recent murders of health-care workers and ominous rumors of the spread of the infection into Rwanda and Tanzania suggest that it may continue for some time.

Prior to the West African outbreak, there existed no effective vaccine or antiviral therapy for Ebola.[129] 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. The abstract of the article in which they reported the fruits of their research follows:

> 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

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[127] Ibid.

[128] 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.

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

> protected animals after challenge. Our data suggest that these vaccine candidates are safe and highly efficacious in a relevant animal model.[130]

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*.[131] 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 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.[132] (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.[133]

The outcome of this story is not entirely happy, however. As the scale of the ongoing outbreak in eastern Congo makes clear, possession of an effective vaccine is not sufficient; it must be administered to people at risk – no easy task in rural subSaharan Africa, particularly in regions beset by violence.[134] And rVSV-ZEBOV is only effective against one strain of the

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[130] Steven M Jones et al., "Live Attenuated Recombinant Vaccine Protects Nonhuman Primates against Ebola and Marburg Viruses," *Nature Medicine* 11 (2005).

[131] See https://www.congress.gov/113/plaws/publ233/PLAW-113publ233.pdf.

[132] 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.

[133] 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) .

[134] The following description of the conditions in the eastern Congo, the site of the most 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

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.[135] 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.[136]

E. Dengue

Like HIV, dengue is caused by a virus. Unlike HIV, it is transmitted from one person to another, not through direct contact with an infected person's fluids, but by a mosquito – specifically, one of two types of mosquito, *Aedes aegypti* and *Aedes albopictus*.[137]

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.[138] 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.[139]

There are four closely related strains (or "serotypes") of the dengue virus.[140] 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

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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.

135 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.

136 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/.

137 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.

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

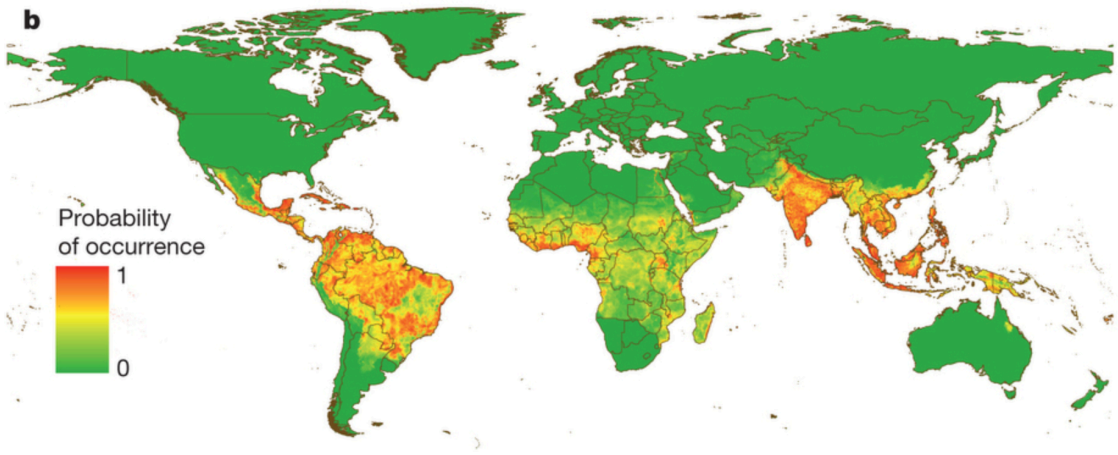
139 See Ngo Thi Nhan et al., "Acute Management of Dengue Shock Syndrome: A Randomized Double-Blind Comparison of 4 Intravenous Fluid Regimens in the First Hour," *Clinical Infectious Diseases* 32 (2001).

140 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).

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.[141]

Like HIV and Ebola, dengue appears to have originally developed in monkeys.[142] When it made the leap to humans is uncertain. A disease that appeared in China as early as the fourth century 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.[143] 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 rebound; and global warming, which has further increased the range of the relevant mosquitos.[144] Figure 11, below, shows the incidence of the disease as of 2010.

Figure 11[145]



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),

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

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

143 See Gubler, "Dengue and Dhf."

144 See ibid.

145 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://gamapserver.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.

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 has been triple the number reported during the previous year, and Argentina expects to have a record number of cases.[146]

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.

Because of the paucity of therapies, efforts to combat dengue are currently focused on two fronts: vector control and the development of the vaccine.[147] The principal vector-control initiatives are: (a) strategies to reduce the populations of mosquitos, particularly in urban areas;[148] (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.[149] Despite these obstacles, several pharmaceutical firms have been working for decades to develop a vaccine. As of 2010, there were nine such ventures underway;[150] by 2015, there were six.[151]

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.[152] But it was sufficiently promising that it was quickly approved for use in Mexico, Brazil, Indonesia, and the Philippines.[153] 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"

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[146] 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.

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

[148] 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/.

[149] See Guzman et al., "Dengue: A Continuing Global Threat," S13.

[150] See ibid.

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

[152] 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.

[153] See Jelmayer, "Brazil Approves Sanofi's Dengue Vaccine."; http://en.sanofi.com/NasdaQ_OMX/local/press_releases/dengvaxia_first_dengue_vaccine_1975899_28-12-2015!11_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.

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.[154]

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 one Dengue infection.[155] The search continues for a more effective – and widely applicable vaccine.

[154] 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/.

[155] "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.

References

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

Afolabi, Muhammed O., Jane U. Adetifa, Egeruan B. Imoukhuede, Nicola K. Viebig, Beate Kampmann, and Kalifa Bojang. "Early Phase Clinical Trials with Human Immunodeficiency Virus-1 and Malaria Vectored Vaccines in the Gambia: Frontline Challenges in Study Design and Implementation." *American Journal of Tropical Medical Hygiene* 90, no. 5 (2014): 908-14.

Antonio, Monica. "Dengvaxia, World's First Dengue Vaccine, Gets Mexican Approval -- What You Need to Know." *Patent Herald*, December 11, 2015.

Barbara, Vanesa. "10 Days of Dengue Fever." *New York Times*, May 1, 2015 2015.

Becker, Alexandra. "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/.

Beer, B., and R. Kurth. "Characteristics of Filoviridae: Marburg and Ebola Viruses." *Naturwissenschaften* 86 (1999): 8-17.

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

Benzaken, Adele S., 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).

Bhatt, Samir, Peter W. Gething, Oliver J. Brady, Jane P. Messina, Andrew W. Farlow, Catherine L. Moyes, John M. Drake*, et al.* "The Global Distribution and Burden of Dengue." *Nature* 496 (2013): 504-07.

Boseley, Sarah, and Jason Burke. "Ebola in the Drc: Everything You Need to Know." *The Guardian* (2019). Published electronically August 1, 2019. https://www.theguardian.com/world/2019/may/15/ebola-in-the-drc-everything-you-need-to-know.

Branswell, Helen. "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/.

Coalition, AIDS Vaccine Advocacy. "Hiv Vaccines: An Introductory Factsheet." 2019.

Control, Centers for Disease. "About Marburg Hemorrhagic Fever." (2014). https://www.cdc.gov/vhf/marburg/about.html.

Corbel, Vincent, Francois Nosten, Kanutcharee Thanispong, Christine Luxemburger, Monthathip Kongmee, and Theeraphap Chareonviriyaphap. "Challenges and Prospects for Dengue and Malaria Control in Thailand, Southeast Asia." *Trends in Parasitology* 29, no. 12 (2013): 623-.

Cumming-Bruce, Nick. "Nigeria Is Free of Ebola, Health Agency Confirms." *New York Times*, October 20, 2014.

de Jong, Bouke C. , Ifedayo Adetifa, Brigitte Walther, Philip Hill, Martin Antonio, Martin Ota, and Richard A. Adegbola. "Diferences between Tuberculosis Cases Infected with Mycobacterium Africanum, West African Type 2, Relative to Euro-American Mycobacterium Tuberculosis: An Update." *FEMS Immunology & Medical Microbiology* 58 (2010): 102-05.

Dheda, Keertan, Tawanda Gumbo, Neel R. Gandhi, Megan Murray, Grant Theron, Zarir Udwadia, G B Migliori, and Robin Warren. "Global Control of Tuberculosis: From Extensively Drug-Resistant to Untreatable Tuberculosis." *Lancet Respiratory Medicine* 2 (2014): 321-38.

Eakins, Sean, and Antony J. Williams. "Curing Tb with Open Science." *Tuberculosis* 94 (2014): 183-85.

EW, Tiermerma. "Natural History of Tuberculosis: Duration and Fatality of Untreated Pulmonary Tuberculosis in Hiv-Negative Patients: A Systematic Review." *PLoS ONE* 6, no. 4 (2011): e17601.

Figtree, Melanie, Rogan Lee, Lisa Bain, Tom Kennedy, Sonia Mackertich, Merrill Urban, Qin Cheng, and Bernard J. Hudson. "Plasmodium Knowlesi in Human, Indonesian Borneo." *Emerging Infectious Diseases* 16, no. 4 (2010): 672-74.

Fox, Maggie. "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.

Gaffney, A. "Regulatory Explainer: Everything You Need to Know About Fda's Priority Review Vouchers." *Regulatory Affairs Professionals Society*, 28 May 2015.

Gatton, Michelle L, Makul Chltnis, Tomas Churcher, 7 Azra C. Ghani Martin J. Donnelly, 8 H. Charles J., 1 Godfray, 9 Fred Gould,1,10 Ian Hastings,11 John Marshall,6 Hilary Ranson,7 Mark Rowland,12 Jeff Shaman,1,13, and and Steve W. Lindsay1. "The Importance of Mosquito Behavioral Adaptations to Malaria Control in Africa." *Evolution* 67, no. 4 (2013): 1218-30.

Gilbert, Jonathan. "Argentina Battles Major Outbreak of Dengue as Mosquito Population Swells." *New York Times*, February 17, 2016.

Good, Michael F. "The Ability to Inoculate Purified Malaria Sporozoites Will Accelerate Vaccine and Drug Discovery." *American Journal of Tropical Medical Hygiene* 91, no. 3 (2014): 437-38.

Grosset, J.H., T.G. Singer, and William R. Bishai. "New Drugs for the Treatment of Tuberculosis: Hope and Reality." *International Journal of Tuberculoisis and Lung Disease* 16, no. 8 (2012): 1005-14.

Gubler, Duane. "Dengue and Dengue Hemorrhagic Fever." *Clinical Microbiology Reviews* 11, no. 3 (1998): 480-96.

Guzman, Maria G., Scott B. Halstead, Harvey Artsob, Philippe Buchy, Jeremy Farrar, Duane J. Gubler, Elizabeth Hunsperger*, et al.* "Dengue: A Continuing Global Threat." *Nature Reviews Microbiology* (2010).

Initiative, Clinton Health Access. "Hiv Market Report: The State of Hiv Treatment, Testing, and Prevention in Low- and Middle-Income Countries." 2019.

Initiative, Malaria Vaccine. "Mvi Portfolio." (2019). https://www.malariavaccine.org/projects/mvi-portfolio.

———. "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.

Jelmayer, Rogerio. "Brazil Approves Sanofi's Dengue Vaccine." *Wall Street Journal*, December 28, 2015.

Jones, Steven M, Heinz Feldmann, Ute Ströher, Joan B Geisbert, Lisa Fernando, Allen Grolla, Hans-Dieter Klenk*, et al.* "Live Attenuated Recombinant Vaccine Protects Nonhuman Primates against Ebola and Marburg Viruses." *Nature Medicine* 11 (2005): 786.

Kelly, J. Daniel, Lee Worden, S. Rae Wannier, and Nicole A. Hoff. "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).

Kitamura, Makiko. "World's First Dengue Vaccine Approved after 20 Years of Research." *Bloomberg Business*, December 9, 2015.

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

Ma, Zhenkun, Christian Lienhardt, Helen McIlleron, and Andrew J Nunn. "Global Tuberculosis Drug Development Pipeline: The Need and the Reality." *Lancet* 375, no. 9731 (2010): 2100-09.

Maharaj, R, J Raman, N Morris, D Moonasar, D N Durrheim, I Seocharan, P Kruger, B Shandukani, and I Kleinschmidt. "Epidemiology of Malaria in South Africa: From Control to Elimination." *South African Medical Journal* 103 (2013): 779-83.

Mbenda, Huguette Gaelle Ngassa, Gauri Awasthi, and Poonam Singh. "Does Malaria Epidemiology Project Cameroon as 'Africa in Miniature'?". *Journal of Bioscience* 39, no. 4 (2014): 727-38.

McNeil, Donald C., Jr. "Nigeria's Actions Seem to Contain Ebola Outbreak." *New York Times*, September 30, 2014.

McNeil, Donald G., Jr. "Drug Companies Are Focusing on the Poor after Decades of Ignoring Them." *New York Times*, June 24, 2019.

Mharakurwaa, Sungano , Philip E. Thuma, Douglas E. Norrisa, Modest Mulengac, Victor Chalwec, James Chipetad, Shungu Munyatie, Susan Mutambuf, and Peter R. Mason. "Malaria Epidemiology and Control in Southern Africa." *Acta Tropica* 121 (2012): 202-06.

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.

Murray, C.J.L., Theo Vos, and Alan Lopez. "Global, Regional, and National Incidence and Mortality for Hiv, Tuberculosis, and Malaria During 1990–2013: A Systematic Analysis for the Global Burden of Disease Study 2013." *Lancet* 384 (2014): 1005-70.

Musumba, Mark, 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): 74-87.

Nhan, Ngo Thi, Cao Xuan Thanh Phuong, Rachel Kneen, Bridget Wills, Nguyen Van My, Nguyen Thi Que Phuong, Chu Van Thien*, 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): 204-13.

Noor, Abdisalan M, Damaris K Kinyoki, Clara W Mundia, Caroline W Kabaria, Jonesmus W Mutua, Victor A Alegana, Ibrahima Socé Fall, and Robert W Snow. "The Changing Risk of Plasmodium Falciparum Malaria Infection in Africa: 2000–10: A Spatial and Temporal Analysis of Transmission Intensity." *The Lancet* 383 (2014).

Normile, Dennis. "Surprising New Dengue Virus Throws a Spanner in Disease Control Efforts." *Science* 342, no. 6157 (2013): 415.

Ojakaa, David I, Jordan D Davis, Mary Matilu, and Sylla Thiam. "Acceptance of a Malaria Vaccine by Caregivers of Sick Children in Kenya." *Malaria Journal* 13 (2014): 172.

Prevention, Centers for Disease Control and. "Epidemiology: Dengue." http://www.cdc.gov/dengue/epidemiology/.

Rosenberg, Tina. "H.I.V. Drugs Cost $75 in Africa, $39,000 in the U.S.. Does It Matter?" *New York Times*, September 18, 2018.

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

Schwatrz, Lauren M., M. Elizabeth Halloran, Anna P. Durbin, and Ira M. Jr. Longini. "The Dengue Vaccine Pipeline: Implications for the Future of Dengue Control." *Vaccine* 33 (2015): 3293-98.

Stylianou, N. "How World's Worst Ebola Outbreak Began with One Boy's Death." *BBC News*, 27 November 2014.

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

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

"The Toll of a Tragedy." *The Economist*, May 5, 2015.

UNAIDS. "Global Hiv & Aids Statistics — 2019 Fact Sheet." (2019). https://www.unaids.org/en/resources/fact-sheet.

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

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

Weintraub, Karen. "Mosquitos Don't Bug Rich Tourists on Marlon Brando's Island. Here's Why That Matters." *STAT* Published electronically March 3, 2016. http://www.statnews.com/2016/03/03/marlon-brando-mosquitoes/.

WHO. "Drug-Resistant Tb: Surveillance and Response." 2014.

———. "Global Tuberculosis Report." 2014.

———. *Global Tuberculosis Report.* 2019.

———. "Global Update on the Health Sector Response to Hiv, 2014." 2014.

———. "Implementing the Stop Tb Strategy: A Handbook for National Tuberculosis Control Programmes." 2008.

———. "Intermittent Preventive Treatment in Pregnancy (Iptp)." (2019). https://www.who.int/malaria/areas/preventive_therapies/pregnancy/en/.

———. "Model List of Essential Medicines." 2013.

———. "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/.

———. "The Stop Tb Strategy: Building on and Enhancing Dots to Meet the Tb-Related Millennium Develpment Goals." 2006.

———. *Treatment of Tuberculosis Guidelines.* 4th ed. Geneva2009.

———. "World Malaria Report." 2019.

———. "World Malaria Report." (2014).

———. "World Malaria Report, 2018." (2018).

Wong, Emily B., Keira A. Cohen, and William R. Bishai. "Rising to the Challenge: New Therapies for Tuberculosis." *Trends in Microbiology* 21, no. 9 (2013): 493-501.

Xing, Zhou, Mangalakumari Jeyanathan, and Fiona Smaill. "New Approaches to Tb Vaccination." *CHEST* 146, no. 3 (2014): 804.

Zimmerman, P.A. "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): e1001685.