# Rethinking Global Pharmaceutical Policy

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## Appendix 4: Dengue

(version 3, December 2024)

Like malaria, dengue is transmitted from one person to another by a mosquito – specifically, one of two types of mosquito, *Aedes aegypti* and *Aedes albopictus*.[1] Unlike malaria, however, it is caused by a virus, rather than a parasite.

The symptoms of the disease vary widely. In a majority of the cases, dengue 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 debilitating, but typically lasts only 10 days and results in no permanent impairment.[2] 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.[3]There are four closely related strains (or "serotypes") of the virus.[4] Infection by one strain confers lifelong immunity to another infection by that strain, but only temporary (roughly two years) of immunity against infection by one of the other strains. A second infection is much more likely to lead to DHF or DSS than a first infection – apparently because of "antibody-dependent enhancement" (ADE), a poorly understood phenomenon.[5]

Like HIV and Ebola, to which we will turn shortly, dengue appears to have originally developed in monkeys.[6] When it made the leap to humans is uncertain. A disease that appeared in China as early as the fourth century A.D. may have been dengue; outbreaks in the French West Indies and Panama in the 17th century and in Indonesia, Egypt, and Philadelphia in the 18th century were probably dengue.[7] 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

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[1] 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.

[2] 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.

[3] 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).

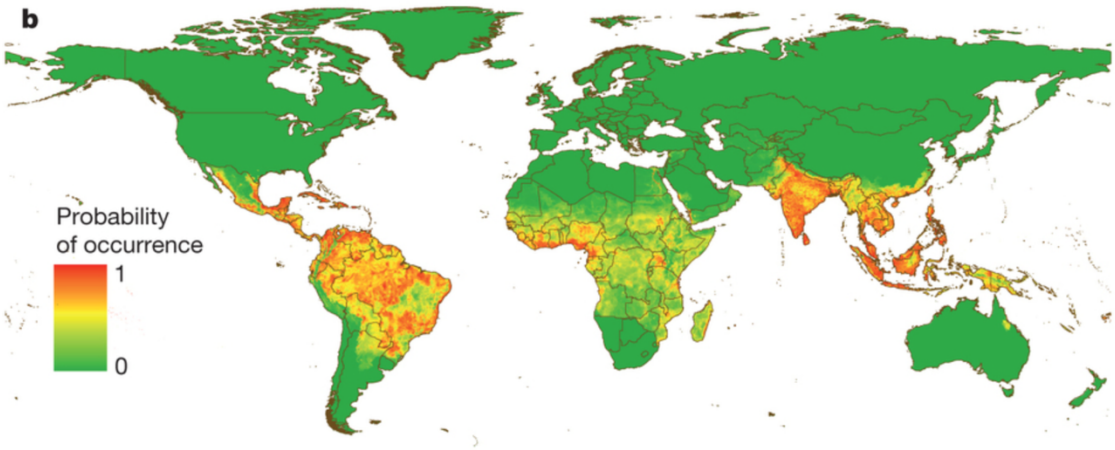
[4] A fifth serotype may have been discovered recently. See Dennis Normile, "Surprising New Dengue Virus Throws a Spanner in Disease Control Efforts," *Science* 342, no. 6157 (2013).

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

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

[7] See Gubler, "Dengue and Dhf."

1960s, which enabled *aegypti* mosquitos to rebound; and global warming, which has further increased the range of the relevant mosquitos.[8] Shown below is the incidence of the disease as of 2010.[9]



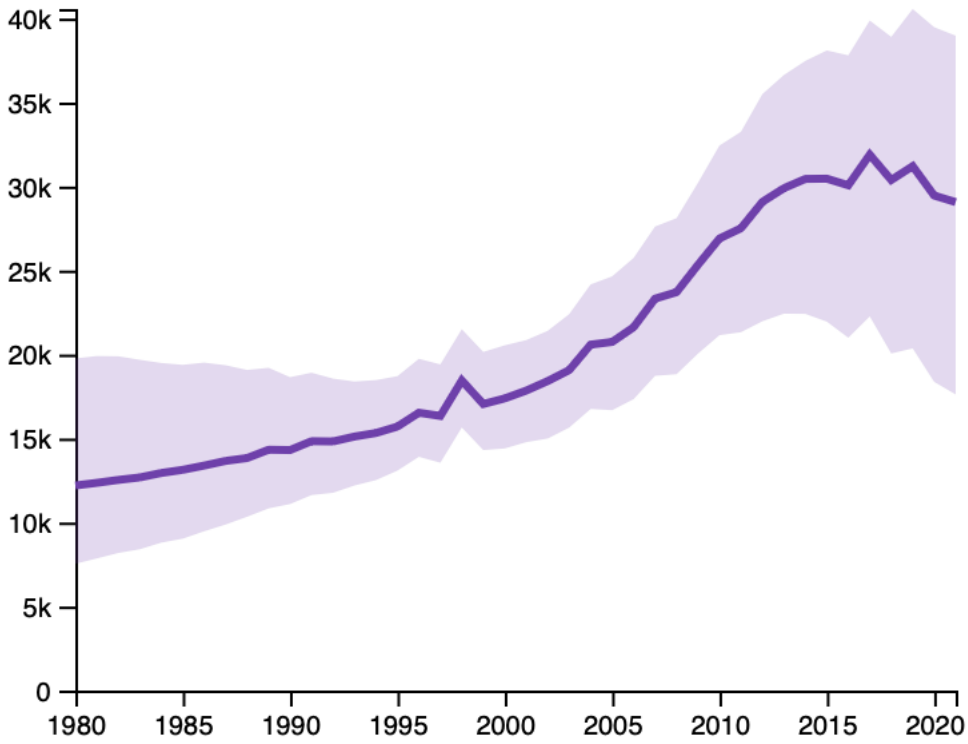

As the map makes clear, dengue is now endemic throughout tropical regions of the world. Today, it infects roughly 390 million people per year. Of that number, roughly 96 million experience symptoms of the disease, and 24,000 die.[10] The number of deaths rose dramatically between 1980 and 2018, declined between 2018 and 2023, and very recently have tipped sharply upward. The following graph shows the long-term trend.[11]

[8] See ibid.

[9] 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.

[10] 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.; WHO, "Global Health Estimates 2021: Estimated Deaths by Cause and Region, 2000-2021," (2024).

[11] This graph contains data derived from the most recent report by the Institute for Health Metrics and Evaluation, https://vizhub.healthdata.org/gbd-results/. The numbers reported by the World Health Organization are somewhat lower, but show the same trend.




The recent change is summarized by the CDC as follows: "Global incidence of dengue in 2024 has been the highest on record for this calendar year.[12]

Asia currently bears the bulk of the burden of the disease. As of 2010, India alone had 34% of the cases, and Asia as a whole had 70%. At that time, only 14% of infections occurred in the Americas (mostly in Brazil and Mexico), but the disease seems to be spreading especially fast in the Western hemisphere. In the (southern) summer of 2015-2016, the number of cases reported in Brazil was triple the number reported during the previous year.[13] More recently, the CDC reported that "[i]n 2024, countries in the Americas have reported a record-breaking number of dengue cases, exceeding the highest number ever recorded in a single year. From January 1 – June 24, 2024, countries in the Americas reported more than 9.7 million dengue cases, twice as many as in all of 2023 (4.6 million cases)." Cases in the United States have thus far been rare, but are increasing.[14]

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[12] Center for Disease Control, "Increased Risk of Dengue Virus Infections in the United States," (2024).

[13] See Gilbert, "Argentina Battles Major Outbreak of Dengue as Mosquito Population Swells."; Jelmayer, "Brazil Approves Sanofi's Dengue Vaccine."

[14] See CDC, "Dengue Cases in the United States" (reporting data as of August 11, 2021, https://www.cdc.gov/dengue/statistics-maps/2021.html; Jane P. Messina et al., "Global Spread of Dengue Virus Types: Mapping the 70 Year History," *Trends in Microbiology* 22, no. 3 (2014); Control, "Increased Risk of Dengue Virus Infections in the United States."; Mary Kekatos, "Dengue Fever Cases Rise to 6,800 in Us Amid 2 New Infections in Los Angeles: Cdc," *ABC News*, October 31, 2024 2024.; Lorenzo Cattarino et al., "Mapping Global Variation in Dengue Transmission Intensity," *Science Translational Medicine* 12, no. 528 (2020).

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 a vaccine.[15] The principal vector-control initiatives are: (a) strategies to reduce the populations of mosquitos, particularly in urban areas;[16] (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.[17] Despite these obstacles, several pharmaceutical firms have been working for decades to develop a vaccine. As of 2010, there were nine such ventures underway;[18] by 2015, there were six.[19]

The most promising of the candidates was "Dengvaxia," a live attenuated vaccine developed by Sanofi using a yellow-fever-vaccine backbone. Early on, it became clear that Dengvaxia was not perfect. In 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.[20] But it was sufficiently promising that it was quickly approved for use in Mexico, Brazil, Indonesia, and the Philippines.[21] Unfortunately, in practice, it proved to have a crucial drawback, which had not come to light in the trials: when administered to a "dengue-naïve" person (i.e., someone who had never been infected by any of the four dengue variants), it produced the ADE effect, mentioned above. In other words, it sharply increased the risk that the person would experience the potentially deadly dengue hemorrhagic fever if subsequently infected with a different variant of the virus. Several patients in the Phillipines died as a result, prompting the

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

[16] 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/.

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

[18] See ibid.

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

[20] 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.

[21] 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.

government to withdraw its approval of Dengvaxia – and initiate criminal proceedings against Sanofi executives.[22]

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.[23] The search continues for a more effective – and widely applicable vaccine.[24]

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[22] 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/.

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

[24] See Sandra Henein et al., "Dengue Vaccine Breakthrough Infections Reveal Properties of Neutralizing Antibodies Linked to Protection," *Journal of Clinical Investigation* 131 (2021).