

Infection: The Health Crisis in the Developing World and What We Should Do About It
(Stanford University Press, forthcoming 2017)

Chapter 1: The Diseases³

2. 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*.⁴

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.⁵ 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.⁶

There are four closely related strains (or “serotypes”) of the dengue virus.⁷ 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,” a poorly understood phenomenon.⁸

¹ WilmerHale Professor of Intellectual Property Law, Harvard University.

² Assistant Professor of Law, University of California at Berkeley.

³ Version 1.0. Updated versions of this document (and of other portions of the book of which it is a part) will be posted periodically at <http://cyber.law.harvard.edu/people/tfisher/Infection.htm>.

⁴ 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.

⁵ An excellent description of a typical case can be found in Vanesa Barbara, “10 Days of Dengue Fever,” *New York Times*, May 1, 2015.

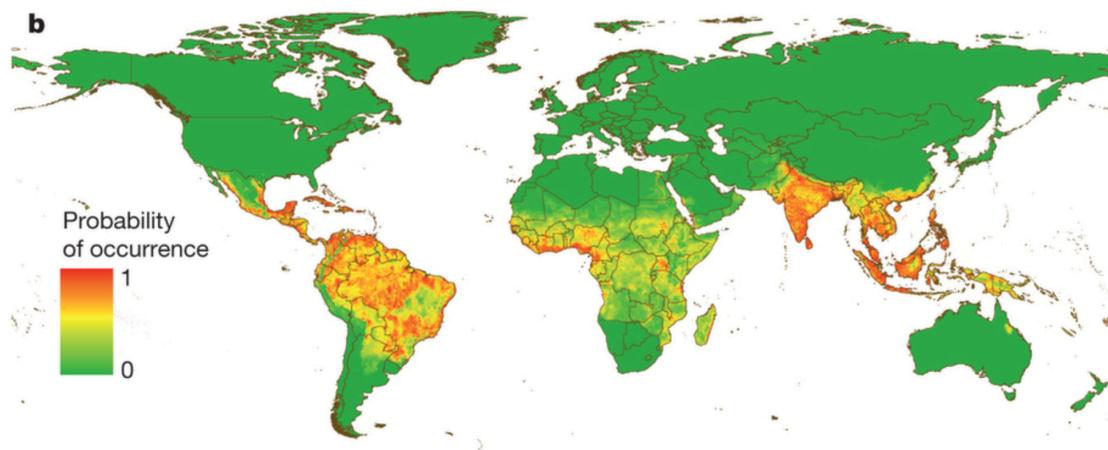
⁶ See Ngo Thi Nhan et al., “Acute Management of Dengue Shock Syndrome: A Randomized Double-Blind Comparison of 4 Intravenous Fluid Regimens in the First Hour,” *Clinical Infectious Diseases* 32 (2001).

⁷ 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).

⁸ See Duane Gubler, “Dengue and Dengue Hemorrhagic Fever,” *Clinical Microbiology Reviews* 11, no. 3 (1998): 487.

Like HIV and Ebola, dengue appears to have originally developed in monkeys.⁹ 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.¹⁰ 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.¹¹ Figure 1, below, shows the incidence of the disease as of 2010.

Figure 1¹²



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

⁹ See Maria G. Guzman et al., "Dengue: A Continuing Global Threat," *Nature Reviews Microbiology* (2010): S7.

¹⁰ See Gubler, "Dengue and Dhf."

¹¹ See *ibid.*

¹² 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>.

has been triple the number reported during the previous year, and Argentina expects to have a record number of cases.¹³

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.¹⁴ The principal vector-control initiatives are: (a) strategies to reduce the populations of mosquitos, particularly in urban areas;¹⁵ (b) protecting people against mosquito bites; and (c) reducing the capacity of mosquito bites to transmit the virus. All three initiatives are discussed in more detail in the subsection (below) on malaria.

Efforts to develop a vaccine have been hampered by several factors: the complex pathology of the diseases; 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.¹⁶ Despite these obstacles, several pharmaceutical firms have been working for decades to develop a vaccine. As of 2010, there were nine such ventures underway;¹⁷ by 2015, there were six.¹⁸ One has now emerged from clinical trials: “Dengvaxia,” a live attenuated vaccine developed by Sanofi using a yellow fever vaccine backbone, has shown great promise. In the past few months, it have been approved for use in Mexico, Brazil, Indonesia, and the Philippines, and will soon be approved for use in India.¹⁹

Although Dengvaxia will likely save thousands of lives and enable millions of people to avoid weeks of misery, for two reasons we should not declare victory quite yet. First, Dengvaxia falls well short of 100% effectiveness. Indeed, in its stage III clinical trials, it

¹³ 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.

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

¹⁵ 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/>.

¹⁶ See Guzman et al., "Dengue: A Continuing Global Threat," S13.

¹⁷ See *ibid.*

¹⁸ See Lauren M. Schwartz et al., "The Dengue Vaccine Pipeline: Implications for the Future of Dengue Control," *Vaccine* 33 (2015): 3294.

¹⁹ 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>.

prevented only 61% of infections (albeit a higher percentage of DHF cases) and is less effective in children under nine years old than in adults.²⁰

Second, Sanofi has thus far refused to make public the prices that it anticipates charging for the vaccine – raising concerns about its accessibility. Sanofi's commendable history of inter-country differential pricing (which we will take up in Chapter 3) provides some assurance that it will engage in socially responsible pricing. However, public reports (not disavowed by Sanofi) that, by 2020, the company could earn up to 1.4 billion euros per year from sales of Dengvaxia are troubling.²¹ Because few of the countries that are most seriously threatened by the disease are wealthy, it is not obvious how the company will be able to generate that much revenue without employing a price structure that places the vaccine beyond the reach of the poorest countries and persons.

In sum, more work must be done, both to develop additional dengue vaccines and to ensure that Dengvaxia and its successors are available to the people who most need them.

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, e.g., Eric Sagonowsky, "Sanofi Preps for 'Profitable' Dengue Vaccine Rollout in 20 Countries," *FiercePharma*, July 20, 2015; "Sanofi Working with Health Authorities on Dengue Vaccine Strategies," *FiercePharma*, January 19, 2016. ("Though he was unable to go into pricing details, [a Sanofi spokesman] said the company is looking to implement a predictable, affordable and sustainable" pricing system that will help it assist the WHO in achieving goals to reduce dengue mortality by at least 50% and morbidity by at least 25% by 2020.")

References

- 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.
- 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.
- Gilbert, Jonathan. "Argentina Battles Major Outbreak of Dengue as Mosquito Population Swells." *New York Times*, February 17, 2016.
- 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).
- Jelmayer, Rogerio. "Brazil Approves Sanofi's Dengue Vaccine." *Wall Street Journal*, December 28, 2015.
- Kitamura, Makiko. "World's First Dengue Vaccine Approved after 20 Years of Research." *Bloomberg Business*, December 9, 2015.
- 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.
- Normile, Dennis. "Surprising New Dengue Virus Throws a Spanner in Disease Control Efforts." *Science* 342, no. 6157 (2013): 415.
- Prevention, Centers for Disease Control and. "Epidemiology: Dengue." <http://www.cdc.gov/dengue/epidemiology/>.
- Sagonowsky, Eric. "Sanofi Preps for 'Profitable' Dengue Vaccine Rollout in 20 Countries." *FiercePharma*, July 20, 2015.
- . "Sanofi Working with Health Authorities on Dengue Vaccine Strategies." *FiercePharma*, January 19, 2016.
- Schwartz, 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.

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/>.