Rethinking Global Pharmaceutical Policy

William Fisher and Talha Syed

Appendix 5: Ebola

(version 1, December 2024)

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).[1] These symptoms typically first appear 8 to 10 days after exposure to the virus.[2] 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.[3]

Key to the virulence of the virus is its surface glycoprotein, which mediates viral entry into host cells.[4] 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.[5]

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.[6] 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.[7] Infections are then transmitted from one person to another through direct contact with: the blood or body fluids of an infected person or

---

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

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

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

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

[5] 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).

[6] 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.

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

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.[8] Currently, the most effective way to halt the spread of the disease is to prevent all such direct contacts. This is typically achieved by isolating infected persons and by ensuring that all health-care providers who come into contact with them wear personal protective equipment.

The disease was first discovered in 1976. Since then, there have been 24 documented outbreaks in humans. Details concerning those outbreaks are presented in the following table and accompanying map.[9]

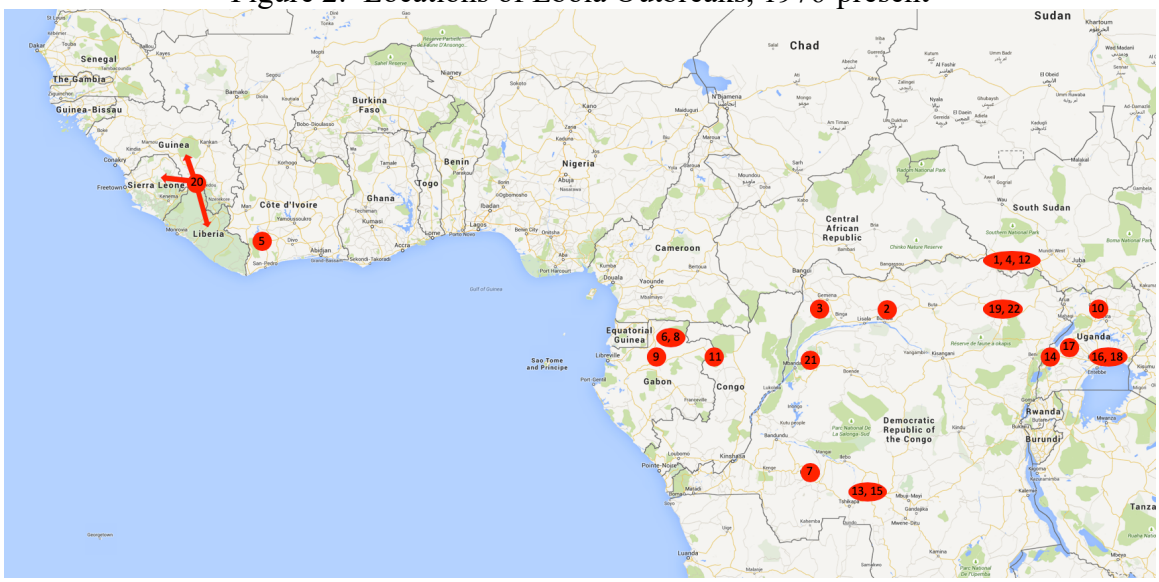
[8] CDC, "Ebola – Transmission"; Gibrilla Deen st al., New England Journal of Medicine, Oct. 14, 2015. There is no evidence that the virus is transmitted through the air or water – or via insects.

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

Figure 1: 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%
23	Guinea	Feb-June, 2021		23	12	52%
24	Cote d'Invoire	August 2021				

Figure 2: 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.[10] 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.[11] 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.[12]

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.[13] By the end of March 2014, the virus had spread to Liberia. Within a few months thereafter, it had spread to Sierra Leone, Nigeria, Senegal, and Mali.[14] 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

[10] 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).

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

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

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

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

virus in West Africa and then returned home.[15] By the spring of 2015, the virus had infected over 27,000 people and claimed over 11,000 lives.[16]

Prior to the West African outbreak, there existed no effective vaccine or antiviral therapy for Ebola.[17] 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.[18] 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*.[19] 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

---

[15] Ibid.

[16] 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.

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

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

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

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.[20]

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.[21]

The outcome of this story is not entirely happy, however. As the persistent outbreaks in various locations in West Africa make clear, the existence of an effective vaccine will not be sufficient to eliminate the disease. In part, this is because the vaccine must be administered to people at risk – no easy task in rural subSaharan Africa, particularly in regions beset by violence.[22] In addition, rVSV-ZEBOV is only effective against one strain of the Ebola virus. As yet, we have no approved vaccines against the other strains – or against the close cousins of Ebola, some of which are at least as dangerous. For example, the Marburg virus, similar to Ebola, has recently been found in bats in Sierra Leone.[23] 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.[24]

---

[20] 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.

[21] 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) .

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

[23] 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.

[24] 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/.