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Infection: The Health Crisis in the Developing World and What We Should Do About It
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Chapter 1, Section A, Part 7: Ebola[4]

The Ebola virus (EBOV) 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).[5] These symptoms typically first appear 8 to 10 days after exposure to the virus.[6] 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 infection typically are themselves infected.[7]

Key to the virulence of the virus is its surface glycoprotein (GP), which mediates viral entry into host cells.[8] The GP 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 hyper-secretion of inflammatory cytokines[9] (also known as a cytokine storm or exaggerated inflammatory response), leading to intravascular coagulation, vascular collapse and multiple organ failure.[10]

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 equatorial forests of central Africa. Active EBOV infection has been detected in three species of fruit bat – *Epomops*

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[4] Version 2.0. 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 has been very helpful in revising the paper. Equally valuable have been written comments submitted by Justin Hughes, Michael Kurilla, Helene Madonick, Quentin Palfrey, Diane Rosenfeld, Judit Rius Sanjuan, and Mark Wu. Updated versions of this document will be posted periodically at http://cyber.law.harvard.edu/people/tfisher/Infection.htm.

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

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

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

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

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

[10] See 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).

franqueti, *Hypsignathus monstrosus*, and *Myonycteris torquata* – and antibodies have been detected in 6 other species. Insectivorous free-tailed bats (*Mops condylurus*) may also be carriers.[11] 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.[12] Infections are transmitted from one person to another through direct contact with: the blood or body fluids of an infected person or corpse; needles or syringes that have been contaminated with body fluids from an infected person; or possibly semen from a man who has recovered from Ebola.[13] 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 20 documented outbreaks in humans. Details concerning those outbreaks are presented in the following table and accompanying map.[14]

[11] 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.

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

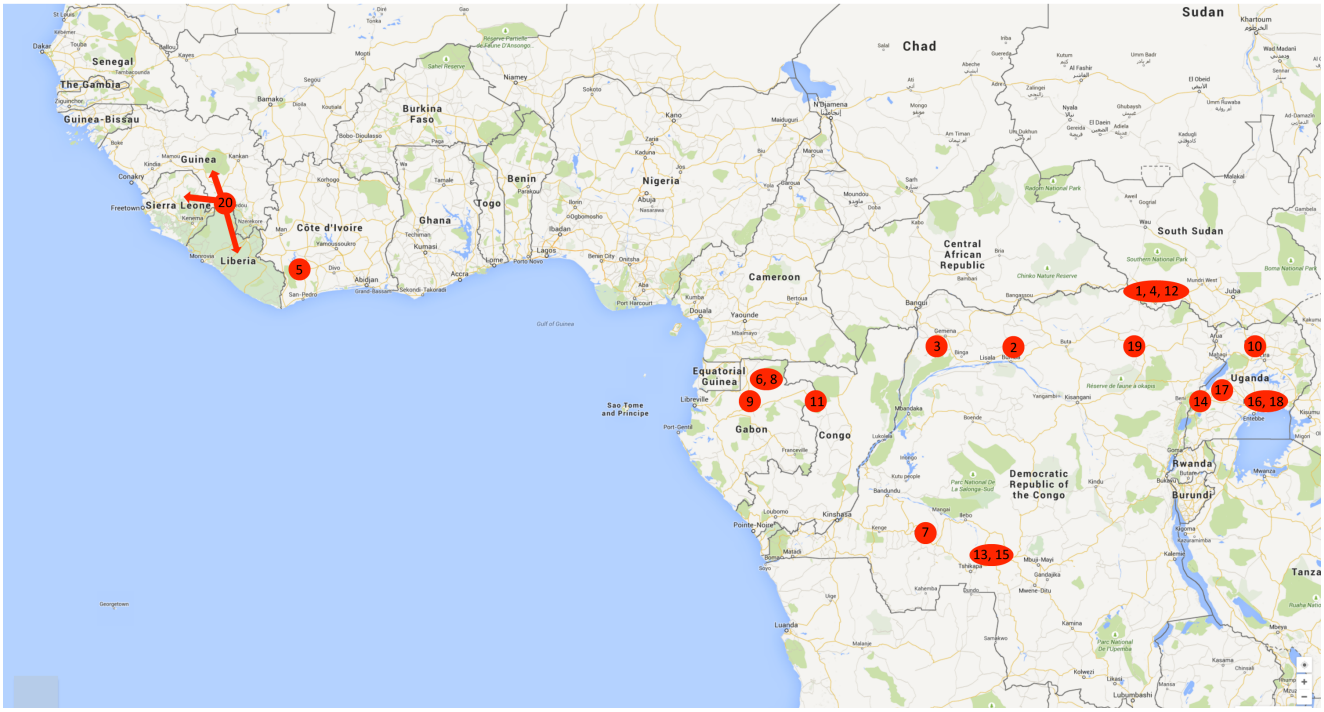
[13] CDC, "Ebola – Transmission"; Gibrilla Deen st al., New England Journal of Medicine, Oct. 14, 2015. There is no evidence that the virus is transmitted through the air or water – or via insects.

[14] 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); and the WHO's Ebola Situation Reports, available at http://apps.who.int/ebola/ebola-situation-reports (last visited October 14, 2015). 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. The case count for the West Africa Outbreak is current as of October 11, 2015.

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, Congo	2007	Zaire	264	187	71%
14	Kabango, Uganda	2007	Bundibugyo	149	37	25%
15	Luebo, Congo	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, Congo	2012	Bundibugyo	57	29	51%
20	Guinea; Sierra Leone; Liberia	2013-2015	Zaire (Makona strain)	28,490	11,312	40%

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.[15] 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.[16] 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.[17]

As the table also reveals, the last of the 20 outbreaks – 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 three-year old sister, Philomene, and their pregnant mother, Sia. 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.[18]

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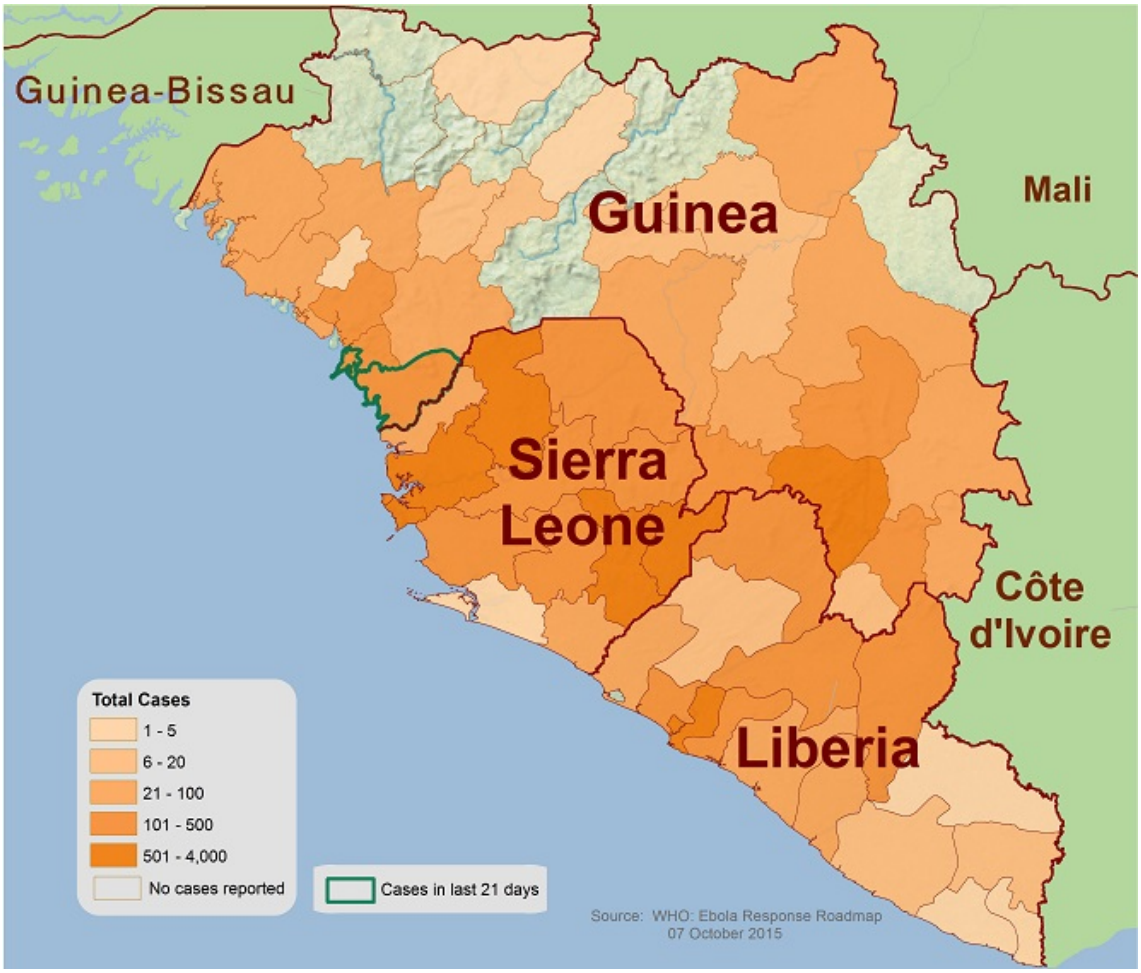
[15] For a comprehensive list of the species and strains – and links to maps of the DNA of each – see Virus Pathogen Resource, "Ebolavirus," available at http://www.viprbrc.org/brc/home.spg?decorator=filo_ebola (last visited June 29, 2015).

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

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

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

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.[19] 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 home.[20] By the spring of 2015, the virus had infected over 27,000 people and claimed over 11,000 lives.[21] The geographic distribution of the outbreak (excluding countries that have reported 20 cases or fewer) is shown in the following map.[22]



The West African Outbreak is not quite finished. On May 9, 2015, the World Health Organization (WHO) declared Liberia free of Ebola-virus transmission, as forty-two days had passed since the corpse of last laboratory-confirmed case had been buried.[23] Since then,

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

[20] Ibid.

[21] See "The Toll of a Tragedy," *The Economist*, May 5, 2015.

[22] Source: http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/distribution-map.html (last visited October 14, 2015).

[23] World Health Organization, Media Centre, "The Ebola outbreak in Liberia is over," 9 May 2015, available at: http://www.who.int/mediacentre/news/statements/2015/liberia-ends-ebola/en/.

however, small numbers of new cases have been reported in all three countries.[24] The majority of new cases in June 2015 arose from well-defined chains of transmission, involving registered, monitored contacts of previous cases. However, roughly 25% arose from unknown sources of infection or were associated with a large number of high-risk contacts, some of whom were untraceable.[25] To reduce the risk that such cases would spark a resurgence of the epidemic, enhanced surveillance and response measures were introduced in both Guinea and Sierra Leone.[26] These tactics may have worked; only 4 new cases (all in Guinea) were reported in the week ending September 30, 2015, and no new cases were reported in the two weeks ending on October 11.[27] But we will not know for sure for another month.

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.[28] Conditions were ripe for an "apocalyptic urban outbreak."[29] 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.[30] Disaster was thus avoided – but barely.

Unless something changes, outbreaks of Ebola in human populations will continue. Hundreds, perhaps thousands of people will die. And the risk of a truly horrific epidemic – of the sort that easily could have occurred in Nigeria – is substantial.

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[24] World Health Organization, Ebola Situation Report, 29 July 2015, available at: http://apps.who.int/ebola/current-situation/ebola-situation-report-29-july-2015.

[25] See WHO Ebola Situation Report, 17 June 2015, available at http://apps.who.int/ebola/current-situation/ebola-situation-report-17-june-2015.

[26] Specifically, in Guinea, health checkpoints have been established in the western prefectures of Boke and Coyah. A 6-day door-to-door case-finding and sensitization campaign commenced in Dubreka on June 7, and investigations are underway to trace a number of high-risk contacts associated with 3 cases recently reported from Conakry. In Sierra Leone, a large-scale operation is planned in the districts of Kambia and Port Loko to terminate the secret movement of cases, contacts, and dead bodies that has aided recent transmission. The operation will involve expanded criteria for identifying and tracing contacts, greater incentives to increase compliance with quarantine measures and encourage the timely reporting and isolation of cases, and increased use of rapid diagnostic tests. Ibid.

[27] See WHO Ebola Situation Report, 26 14 October 2015, available at http://apps.who.int/ebola/ebola-situation-reports.

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

[29] WHO, "Nigeria is Now Free of Ebola Virus Transmission," 20 October 2014, http://www.who.int/mediacentre/news/ebola/20-october-2014/en/.

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

How might we reduce the hazard? The ideal scenario would of course be to eradicate the Ebola virus altogether – as we have done with the smallpox virus.[31] Unfortunately, that is probably infeasible. Unlike smallpox, the Ebola virus appears to have a tolerant animal host: the bats endemic to the forests of central and western Africa. Neither eliminating all of the bats nor purging them of the virus is practicable. At least for the immediate future, therefore, the Ebola virus is here to stay.

More promising is the possibility of preventing transmission of the virus from bats to humans – either directly, or indirectly via infected primates. Educating people concerning the dangers associated with contacting bats or eating potentially contaminated bushmeat could certainly reduce the frequency of transmission. For example, the World Health Organization recommends: "Animals should be handled with gloves and other appropriate protective clothing. Animal products (blood and meat) should be thoroughly cooked before consumption."[32] Unfortunately, because many contacts with infected animals appear to be inadvertent, even universal compliance with these guidelines would not halt the disease altogether. In any event, universal compliance is too much to hope for.

Next, we could try to prevent inter-human transmissions. This is the approach that has enabled us to stop each of the outbreaks to date – and made it possible to prevent epidemics in Nigeria, Europe, and the United States. Appropriately, much effort is currently concentrated on developing technologies (such as protective gear for health workers) and protocols (such as avoiding contact with corpses during burial rituals) that would enable us to stop inter-human transmissions more reliably and swiftly. Equally crucial is strengthening the public-health systems of the affected countries, which (among other things) is essential to the deployment of those technologies and to educating people in the techniques they might employ to avoid infection. The financial and logistical obstacles that must be overcome to implement fully this approach are high, however. And such systems will never be perfect.

This brings us, finally, to the potential role of pharmaceutical products. As the Introduction demonstrated, in the past we have successfully suppressed infectious diseases by developing therapies that cure them – and, better yet, by creating and disseminating widely vaccines that prevent them. The potential benefits that would accrue from application of the same approach to Ebola are obvious. To date, however, we have failed to do so. No effective vaccine or antiviral therapy for Ebola has yet been developed.[33] Why not?

There are five possible explanations. First, the scientific challenge might be too formidable. Infectious diseases vary radically in the difficulties they present to scientists seeking to develop therapies and, in particular, vaccines. Some succumb easily to current

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[31] WHO, "The Smallpox Eradication Programme – SEP (1966-1980)," http://www.who.int/features/2010/smallpox/en/.

[32] WHO, "Ebola Virus Disease," http://www.who.int/mediacentre/factsheets/fs103/en/ (last visited, June 13 2015).

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

technologies. Others are much more hardy. An example of the latter, as we have seen, is HIV. Conceivably, the Ebola virus might be similarly stubborn.

This is possible, but unlikely. It is surely true that research on Ebola is difficult and expensive. It can only be done in a BioSafety Level 4 facility, which costs over $150 million to build and over $15 million per year to operate. However, the scientific challenges to development of an effective vaccine are not insurmountable – surely lower than those associated with HIV. 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 protected animals after challenge. Our data suggest that these vaccine candidates are safe and highly efficacious in a relevant animal model.[34]

The researchers recommended that clinical trials of the two vaccine candidates begin promptly. That this never occurred suggests the second of the five possible explanations: Perhaps clinical trials of Ebola vaccines are too difficult to arrange. Demonstration of the efficacy of a vaccine for a virus requires (at a minimum) administering the vaccine to a group of people who then are exposed to the virus. Prior to the West African Outbreak, Ebola was rare; finding a group of people who would be naturally exposed to the virus was thus difficult. The severity of the disease that Ebola causes, and the absence of a cure, would make it extremely difficult (and ethically problematic) to recruit people willing to take the vaccine and then voluntarily expose themselves to the virus. In short, perhaps clinical trials are infeasible.

This explanation is more plausible than the first, but on reflection also seems incomplete. As Figure __, above, shows, since 1976 there has been an outbreak of Ebola roughly every two years. Excluding the recent West African Outbreak, each has infected an average of 126 people. Each has been highly localized; thus, the population placed at risk of infection has been easy to identify. And each has taken at least a few months to contain. While the public-health initiatives that eventually contained a given outbreak were being

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

implemented, it would have been feasible to administer a vaccine candidate to a subset of the persons in the region who were vulnerable to infection.[35] To be sure, conducting a trial under these circumstances would have been costly, would have necessitated obtaining in advance the permission of the relevant governments, and would have required navigating some tricky ethical shoals – but these impediments could have (and indeed have since) been overcome.

This brings us to the third hypothesis: developing and testing a vaccine may have been practicable, but would surely have been expensive. The pharmaceutical firms on which we rely for the development and testing of most drugs may well have concluded that the potential revenue from an Ebola vaccine would be insufficient to cover those costs, particularly when taking into account the risk of failure. Until 2013, all of the outbreaks had been confined to poor countries in central and western Africa. The revenue that a firm could have collected from the governments of those countries (or from private health-care systems or individuals within those countries) in return for supplying them with an efficacious vaccine would have been modest – likely insufficient to warrant undertaking the project.

This is the explanation to which most analysts of Ebola subscribe. This is the primary reason, they suggest, why the vaccine candidate developed by the Canadian researchers was never tested.[36] And it also explains why, they argue, few other research initiatives were launched prior to the latest outbreak.[37]

This third explanation does indeed seem powerful – but only in accounting for the failure of private pharmaceutical firms to undertake, on their own, the development of a vaccine. Its weakness is that it fails to take into account the complex set of institutions that participate in the identification, funding, and conduct of drug-development projects that have significant public-health implications. The pharmaceutical firms, although key actors, are by no means the only members of the drug-development ecosystem. With growing frequency, they collaborate with other institutions: international organizations (such as the World Health Organization and UNICEF); developed-countries governments and their subdivisions (such as USAID, the NIH, and DFID); nongovernmental organizations (such as the Gates Foundation, the Clinton Foundation, and the Wellcome Trust); universities (such as Yale, Oxford, and Vanderbilt); and advocacy organizations (such as Médecins Sans Frontières and Knowledge Ecology International). Observing that no pharmaceutical firm, on its own, had an economic incentive to develop and test an Ebola vaccine is thus

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[35] Indeed, a variant of this technique was recently employed successfully in a promising test of the VSV-EBOV vaccine candidate in Guinea (discussed in more detail in Part III of this essay). See Ana Maria Henao-Restrepo et al., "Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial," *The Lancet*, July 31, 2015, available at http://www.thelancet.com/pb/assets/raw/Lancet/pdfs/S0140673615611175.pdf ("For this open-label, cluster-randomised ring vaccination trial, suspected cases of Ebola virus disease in Basse-Guinée (Guinea, west Africa) were independently ascertained by Ebola response teams as part of a national surveillance system. After laboratory confirmation of a new case, clusters of all contacts and contacts of contacts were defined and randomly allocated 1:1 to immediate vaccination or delayed (21 days later) vaccination with rVSV-ZEBOV….")

[36] See, e.g., D. Grady, "Ebola Vaccine, Ready for Test, Sat on the Shelf," *New York Times*, October 23, 2014.

[37] See, e.g., J. Surowiecki, "Ebolanomics," *The New Yorker*, August 25, 2014.

insufficient to account for our collective failure to produce one. One must also explain why none of the other players in this complex ecosystem – alone or in combination – undertook to initiate or support the necessary research and development.

Two possibilities come to mind. (These represent, respectively, the fourth and fifth hypotheses.) The more obvious possibility is that Ebola slipped through the cracks. Coordination among the various players enumerated above is ad-hoc; they frequently consult with one another informally and sometimes work closely together on individual projects (such as the GAVI Vaccine Alliance[38]), but there currently exists no mechanism that would enable them collectively to decide which potential research initiatives are most needed and promising – and then to apportion responsibility for pursuing and funding them. Under these conditions, it would not be surprising if no single decision-maker focused on the threat presented by Ebola and the need to counter it.

Although lack of coordination among the relevant players most likely contributed to the slow pace of Ebola research, two factors suggest that it too cannot be a complete explanation for our collective failure to secure an effective vaccine or drug. First, the efforts of the Soviet Union during the Cold War to "weaponize" the virus[39] raised its profile among decisionmakers in at least some branches of the U.S. government. Second, as will become apparent in Part III, officials in the NIH have been trying for some years to nudge forward research in this field.

The other possibility is that one or more (perhaps all) of the decision-makers did focus on the threat posed by Ebola – and concluded that effort and money would be better devoted to other diseases. Bear in mind that, until 2013, most of the Ebola outbreaks had been modest in scale, and none had killed more than 300 people. As the Introduction demonstrated – and as the remainder this chapter will confirm -- many of the other infectious diseases that were then ravaging the developing world were sickening and killing vastly larger numbers. For many of these diseases, there were (and still are) no effective vaccines. Unless developing and testing potential vaccines for them would have been substantially harder (and thus more expensive) than developing and testing an Ebola vaccine, it might have made good sense, from a utilitarian standpoint, for the decision-makers to devote their limited resources to the scourges with the biggest footprints.

We will return to this array of possible explanations in Part IV, when we take up the question of how our drug-development systems might be reformed. Beforehand, however, we must consider the ways in which the West African Outbreak changed the landscape.

The scale and visibility of the recent epidemic in Guinea, Liberia, and Sierra Leone, combined with increased appreciation of the risk that Ebola could spread to the United States and Europe, suddenly altered the calculations of many players in the drug-development ecosystem. Several pharmaceutical firms commenced or revived projects to

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[38] See "GAVI's Partnership Model," http://www.gavi.org/about/gavis-partnership-model/ (last visited June 28, 2015).

[39] See Dina Fine Maron, "Weaponized Ebola: Is It Really a Bioterror Threat?," Scientific American, September 25, 2014, available at http://www.scientificamerican.com/article/weaponized-ebola-is-it-really-a-bioterror-threat/.

develop Ebola vaccines or therapies. Agencies of the governments of several wealthy countries contributed substantial supplementary funding to those projects. Finally, 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*.[40] 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.[41]

To date, 12 vaccine candidates and 9 therapy candidates have emerged from this surge of activity and investment. The status of each of these projects is described below.

Vaccines

VSV-EBOV

VSV-EBOV is the vaccine, discussed above, originally discovered by researchers at the Public Health Agency of Canada's National Microbiology Laboratory in Winnipeg. It is based on the recombinant vesicular stomatitis virus (rVSV), which has been genetically engineered to express the glycoprotein of the Zaire strain of Ebola in order to provoke an immune response.

In 2010, VSV-EBOV was licensed to Iowa-based NewLink Genetics (NewLink) in return for a milestone payment of $205,000.[42] During the next four years, representatives of the NIH and the Department of Defense spent considerable time discussing possible ways of conducting the preclinical safety and IND enabling studies that must be completed before human clinical trials are commenced – but were unable to move the ball forward. In October 2014, after the severity of the West African Outbreak became apparent, the Government of Canada shipped 800 vials of VSV-EBOV to the WHO in Geneva. The WHO then entrusted the donated vials to the Hôpitaux Universitaires de Genève for both storage and clinical testing in Europe and Africa.[43]

In November 2014, NewLink received an upfront payment of $30 million (followed by a milestone payment of $20 million in February 2015) in an exclusive worldwide license and collaboration agreement with Merck Sharp & Dohme (Merck) to develop and commercialize the vaccine. Under the terms of the agreement, Merck will be granted

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

[41] 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.

[42] Walkom, T. "The strange tale of Canada's Ebola vaccine", *The Star,* 25 November 2014, available at: http://www.thestar.com/news/canada/2014/11/25/the_strange_tale_of_canadas_ebola_vaccine_walkom.html.

[43] Public Health Agency of Canada, Fact Sheet – VSV-EBOV, February 18, 2015, available: http://www.phac-aspc.gc.ca/id-mi/vsv-ebov-fs-eng.php.

exclusive rights to VSV-EBOV and any follow-on products.[44] NewLink may earn royalties on sales of the vaccine in certain countries if the vaccine is approved and successfully commercialized.[45] However, it will not receive royalties on sales to African countries and other low-income nations.[46]

In December 2014, NewLink's subsidiary, BioProtection Systems, received a $30 million contract from the Biomedical Advanced Research and Development Authority (BARDA) of the United States Department of Health and Human Services (HHS) to support the manufacture and clinical development of VSV-EBOV.[47] The contract duration is 14 months; if extended by 10 months, BioProtection Systems will receive an additional $41 million.[48] Under the agreement, BioProtection Systems will conduct clinical trials to determine the lowest dose at which the vaccine generates an effective immune response.[49] The company will also attempt to develop a more robust and reproducible vaccine manufacturing process.[50] The contract includes an option to scale-up manufacturing from pilot scale used in clinical trials to commercial scale.[51] In the meantime, BARDA will support the development of vaccine formulations to improve productivity and stability so that the vaccine does not have to be kept frozen, making it easier to transport, store, and use in West Africa.[52]

Preliminary Phase I studies conducted in the United States to assess the safety, reactogenicity, and immunogenicity of VSV-EBOV yielded positive results. All vaccinated volunteers produced neutralizing antibodies within 28 days of vaccination with only mild side-effects.[53] Live viral vaccines generally confer long-lasting immunity; however, data on the duration of the protective response after vaccination with VSV-EBOV is currently

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[44] Schnirring, L. "NewLink, Merck deal boosts prospects for Ebola vaccine," *CIDRAP News*, Nov. 24, 2014, available at: http://www.cidrap.umn.edu/news-perspective/2014/11/newlink-merck-deal-boosts-prospects-ebola-vaccine.

[45] NewLink Genetics Annual Report for year ended December 31, 2014. See http://www.sec.gov/Archives/edgar/data/1126234/000112623415000054/nlnk-20141231x10k.htm.

[46] Schnirring, L. "NewLink, Merck deal boosts prospects for Ebola vaccine," *CIDRAP News*, Nov. 24, 2014, available at: http://www.cidrap.umn.edu/news-perspective/2014/11/newlink-merck-deal-boosts-prospects-ebola-vaccine.

[47] NewLink Genetics Press Release, Dec 22, 2014, available at: http://investors.linkp.com/releasedetail.cfm?releaseid=888640.

[48] United States Department of Health & Human Services, "HHS supports efforts to speed Ebola vaccine delivery," News Release, December 23, 2014, available at: http://www.hhs.gov/news/press/2014pres/12/20141223a.html.

[49] Ibid.

[50] Ibid.

[51] Ibid.

[52] United States Department of Health & Human Services, "HHS supports efforts to speed Ebola vaccine delivery," News Release, December 23, 2014, available at: http://www.hhs.gov/news/press/2014pres/12/20141223a.html.

[53] See J.A. Regules, "A Recombinant Vesicular Stomatitis Virus Ebola Vaccine – Preliminary Report," *New England Journal of Medicine*.

limited.[54] The vaccine has demonstrated efficacy in post-exposure treatment in nonhuman primate models[55] when it is administered 30 minutes to 24 hours after infection.[56]

On the basis of the promising Phase I data (and additional clinical and preclinical data), the VSV-EBOV vaccine was selected for inclusion in the following Phase II and Phase III clinical trials:[57]

a) Partnership for Research on Ebola Vaccines in Liberia (PREVAIL) trial: a Phase II/III randomized, double-blind, controlled, three-arm clinical trial being conducted on approximately 27,000 men and women in Monrovia, Liberia. The estimated completion date for this study is June 2016.[58] Initial results are promising.[59]
b) Phase III cluster-based, non-blind, individually randomized trial in Sierra Leone, sponsored by the US Centers for Disease Control and Prevention and the Ministry of Health of Sierra Leone. This trial began on April 9, 2015 and is expected to be completed by September 2016.[60] The Sierra Leone Consortium - Trial to Introduce a Vaccine against Ebola (STRIVE) - plans to enroll up to 6000 frontline workers in Freetown, Bombali, Port Loko, and Tonkolili. Approximately 90 have been vaccinated thus far.[61]
c) Phase III efficacy study in Guinea (sponsored by the WHO, the Ministry of Health Guinea, Médecins Sans Frontières, Epicentre, and the Norwegian Institute of Public Health). Interim results of the trial became available at the end of July 2015 – and are extremely promising.[62] The vaccine demonstrated 100% efficacy when delivered by ring vaccination. No vaccinee developed symptoms more than 6 days post vaccination, irrespective of whether they were vaccinated immediately, or after a 21-day delay.[63] The trial will now be continued without randomization, to ensure the immediate vaccination of any new clusters of people in contact with a confirmed case of Ebola. The trial may also be expanded to include participants under 18 years of age.[64]

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[54] See ibid.

[55] See A. Marzi, "Vesicular Stomatitis Virus-Based Ebola Vaccines with Improved Cross-Protective Efficacy," *Journal of Infectious Diseases* 204, no. Supplement 3 (2011).

[56] See Regules, "Recombinant Vsv-Ebov."

[57] See ibid.

[58] ClinicalTrials.gov, Partnership for Research on Ebola Vaccines in Liberia, # NCT02344407, available at: https://clinicaltrials.gov/ct2/show/study/NCT02344407?term=NCT02344407&rank=1.

[59] NIH, "Ebola test vaccines appear safe in Phase 2 Liberian clinical trial," March 26, 2015, available at: http://www.nih.gov/news/health/mar2015/niaid-26a.htm.

[60] ClinicalTrials.gov, Sierra Leone Trial to Introduce a Vaccine Against Ebola, #NCT02378753, available at: https://clinicaltrials.gov/ct2/show/results/NCT02378753?term=sierra+leone&rank=1

[61] World Health Organization, "News on vaccines, therapies, diagnostics", 22 April 2015, available at: http://www.who.int/medicines/ebola-treatment/ebola-r_d-newsletter-april.pdf.

[62] Ana Maria Henao-Restrepo et al., "Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial," *The Lancet*, July 31, 2015, available at http://www.thelancet.com/pb/assets/raw/Lancet/pdfs/S0140673615611175.pdf.

[63] Ibid.

[64] Global Biodefense, "100 Percent Efficacy Shown for VSV-EBOV Ebola Vaccine", July 31, 2015, available at http://globalbiodefense.com/2015/07/31/100-percent-efficacy-shown-for-vsv-ebov-ebola-vaccine/

Meanwhile, VSV-EBOV continues to be tested in additional Phase I trials. For example, a Phase I trial is currently being conducted by Dalhousie University, in collaboration with NewLink and the Canadian Institutes of Health Research (CIHR), to assess the safety, tolerability, and immunogenicity of VSV-ZEBOV in healthy adults aged 18-65. The expected completion date is November 2015.[65] Another Phase I study is being conducted to evaluate the safety and immunogenicity of VSV-ZEBOV in healthy adult volunteers in Kilifi, Kenya, as part of the WHO-led VEBCON consortium. The study is designed to establish the safety, tolerability and immunogenicity of VSV-ZEBOV for the first time in sub-Saharan African populations. The investigators intend to vaccinate 40 volunteers in Kenya. The study is sponsored by the University of Oxford and is expected to be completed by December 2015.[66]

cAd3-EBO-Z

cAd3-EBO is a bivalent vaccine derived from a recombinant chimpanzee adenovirus type 3, genetically engineered to encode glycoprotein antigens from the Zaire and Sudan strains of the Ebola virus. In September 2014, a Phase I, dose-escalation, open-label trial of cAd3-EBO in twenty healthy adults yielded positive results. Glycoprotein-specific antibodies were induced in all 20 participants, with reactogenicity and immunogenicity being dose-dependent.[67]

The monovalent form of the vaccine, cAd3-EBOZ, only offers protection against the Zaire strain and is currently being studied in the following trials:

a) a Phase I/II double-blind, randomized, placebo-controlled, safety and immunogenicity, dose-finding trial in healthy adults in Switzerland (estimated completion: September 2015);[68]
b) A Phase IB, open-label clinical trial to evaluate the safety, tolerability, and immunogenicity of the vaccine in healthy adults in Kampala, Uganda (estimated completion: December 2016);
c) the PREVAIL trial in Liberia (estimated completion: June 2016);[69]
d) a Phase I/1b, open-label, dose-escalation trial to evaluate the saftey, tolerability and immunogenicity of cAd3-EBOZ in healthy adults aged 18-65 in the United States (estimated completion date: August 2016);[70] and

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[65] ClinicalTrials.gov, "Phase I Trial to Assess the Safety, Tolerability and Immunogenicity of a Ebola Virus Vaccine (VSVΔG-ZEBOV)", # NCT02374385, available at: https://clinicaltrials.gov/ct2/show/study/NCT02374385?term=VSV%CE%94G-ZEBOV&rank=1.

[66] ClinicalTrials.gov, "A Study to Find Out if the New Ebola Vaccine is Safe and Stimulates Immunity That Might Protect Adults in Kilifi, Kenya", # NCT02296983, available at: https://clinicaltrials.gov/ct2/show/results/NCT02296983?term=VSV%CE%94G-ZEBOV&rank=3.

[67] See Ledgerwood, "Chimpanzee Adenovirus Vector Ebola Vaccine."

[68] ClinicalTrials.gov, "A Clinical Trial on the Candidate Vaccine cAd3-EBOZ in Healthy Adults in Switzerland", # NCT02289027, available at: https://clinicaltrials.gov/ct2/show/NCT02289027?term=cAd3-EBOZ&rank=1.

[69] NIH, "Ebola test vaccines appear safe in Phase 2 Liberian clinical trial," March 26, 2015, available at: http://www.nih.gov/news/health/mar2015/niaid-26a.htm. For details on this trial, see the text accompanying note 58, supra.

e) a Phase I clinical trial as a priming vaccine (with Bavarian Nordic's MVA-BN Filo vaccine as the boost vaccine) in a prime-boost regimen.[71]

Both the bivalent and multivalent forms of the vaccine are being developed by GlaxoSmithKline (GSK) in conjunction with the National Institutes of Health (NIH) and the National Institute of Allergy and Infectious Disease (NIAID). The cAd3-EBOZ vaccine requires a boost with an MVA/ZEBOV vector for protection past 6 months.[72]

In August 2014, an international consortium was assembled to accelerate collaborative multi-site trials of pipeline Ebola vaccines. A $4.6 million grant was provided by the Wellcome Trust, the Medical Research Council (MRC), and the UK Department for International Development (DFID) to enable a team led by Professor Adrian Hill of the Jenner Institute at the University of Oxford to start testing cAd3-EBOZ in the UK, while the NIAID ran similar trials in the US. A portion of the consortium's funding supported the manufacture by GSK of approximately 20,000 additional doses of the vaccine in preparation for the next stage of clinical testing if the first trials were successful.[73]

In October 2014, the Bill & Melinda Gates Foundation agreed to provide GSK with approximately $3 million in additional funding to accelerate the development of cAd3-EBOZ, including the manufacture of a second tranche of the vaccine to enable rapid progression to the next phase of testing.[74]

In December 2014, BARDA awarded GSK a 31-month contract worth $12.9 million, with an option to raise the amount by $16,000.[75] The money will be used to establish the initial material needed to start manufacturing the vaccine.[76] Under the agreement, GSK will establish and validate master cell banks and virus seeds, which are the initial manufacturing materials. The company will also expand its manufacturing process from the current pilot system, which produces thousands of vaccine doses for early development activities, to a commercial system, capable of producing millions of doses.[77] (The manufacturing scale-up of any vaccine is a complex process, usually undertaken in later phases of development as new drugs and vaccines move through clinical trials and are prepared for the commercial market. Normally this takes two to three years. In the GSK

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[70] ClinicalTrials.gov, Safety, Tolerability, and Immunogenicity of the Ebola Chimpanzee Adenovirus Vector Vaccine (cAd3-EBO), VRC-EBOADC069-00-VP, in Healthy Adults, # NCT02231866, available at: https://clinicaltrials.gov/ct2/show/results/NCT02231866?term=cAd3-EBOZ&rank=3.

[71] ClinicalTrials.gov, A Study to Assess New Ebola Vaccines, cAd3-EBO Z and MVA-BN® Filo, # NCT02240875, available at: https://clinicaltrials.gov/ct2/show/study/NCT02240875.

[72] See C. Mire, "Single-Dose Attenuated Vesiculovax Vaccines Protect Primates against Ebola Makona Virus," *Nature* 520

[73] GlaxoSmithKline, "Forming public partnerships," available at: http://us.gsk.com/en-us/our-stories/health-for-all/our-contribution-to-the-fight-against-ebola/forming-public-partnerships/.

[74] Ibid.

[75] *NewLink, GSK Get U.S. Funding for Faster Development of Ebola Vaccines*, REUTERS (December 23, 2014), http://www.reuters.com/article/2014/12/23/us-health-ebola-vaccine-idUSKBN0K11VW20141223.

[76] Ibid.

[77] FirstWordPharma, Press Release, "HHS supports efforts to speed Ebola vaccine delivery", December 24, 2014, available at: http://www.firstwordpharma.com/node/1253470?tsid=5#axzz3bNGX05Zb.

project, the scale-up will be compressed to less than a year.[78]) In the meantime, BARDA will support the development of vaccine formulations to improve productivity and stability so that the vaccine does not have to be kept frozen, making it easier to transport, store, and use in West Africa.[79]

The European Commission has provided approximately $19.8 million and the Swiss Government has contributed approximately $1.98 million to help accelerate the development of cAd3-EBOZ.[80]

VesiculoVax

Profectus BioSciences Inc. (Profectus) has developed the VesiculoVax vaccine delivery system to address infectious diseases where the rapid induction of neutralizing antibodies is needed to protect against viruses. The VesiculoVax vaccine for both pre- and post-exposure protection against the hemorrhagic diseases caused by Ebola and Marburg viruses uses vesicular stomatitis virus (rVSV) as a vehicle – the same vehicle used for the vaccine candidates originally developed by the Canadian researchers. The rVSV-based vectors are engineered to express the surface glycoproteins that the Ebola and Marburg viruses use to recognize, bind, and infect a host cell.[81] Work on this candidate has been supported by a series of grants:

a) In April 2012, Profectus and the Galveston National Laboratory (GNL) at the University of Texas Medical Branch at Galveston (UTMB) received a five-year $5.4 million grant from the NIAID to support the development of a trivalent vaccine to protect against all major strains of Ebola and Marburg viruses.[82]
b) In March 2014, the GNL, Profectus, Tekmira Pharmaceuticals, and the Vanderbilt University Medical Center were awarded $26 million by the NIAID to develop combination treatments for infection by Ebola and Marburg viruses.[83]
c) In July 2014, Profectus and the GNL were awarded a three-year $8.5M grant from the DOD/JVAP to develop a trivalent VesiculoVax-vectored vaccine to protect against aerosol exposure to all major strains of the Ebola and Marburg viruses. The trivalent vaccine is currently being tested in both pre-exposure and post-exposure studies with non-human primates.[84]
d) In October 2014, Profectus received a one-year contract from BARDA for the advancement of VesiculoVax into human clinical studies. The one-year contract will provide $5.8 million in funding to conduct safety studies and to manufacture doses for use in Phase I clinical studies. The contract can be extended to a total of 13

[78] Ibid.

[79] Ibid.

[80] GlaxoSmithKline, "Forming public partnerships."

[81] Moynihan, M. Press Release, Profectus BioSciences Inc, October 22, 2014, available at: http://www.profectusbiosciences.net/pdfs/releases/2014%201022%20Profectus%20Ebola%20DoD.pdf.

[82] Ibid.

[83] Profectus BioSciences Inc, Press Release, October 31, 2014, available at: http://www.profectusbiosciences.net/pdfs/releases/2014%201031%20Profectus%20DoD%20Tri-V%20Ebola%20Contract.pdf.

[84] Ibid.

months and $8.6 million. Profectus will then apply to the FDA for an Investigational New Drug (IND) designation, which would allow initiation of human clinical trials.[85]

e) In October 2014, Profectus also received $9.5 million in funding from the Department of Defense (DoD) to support the manufacture, preclinical testing, and Phase I testing of a trivalent VesiculoVax-vectored Ebola/Marburg vaccine.[86]

Preclinical studies conducted by investigators from the GNL Medical Branch (UTMB) at Galveston and the NIH have shown that a single dose of the VesiculoVax Ebola vaccine is able to protect non-human primates against lethal challenge with the Zaire and Sudan species of Ebola virus.[87] A trivalent vaccine to protect against all filoviruses has also entered non-human primate testing with financial support from the NIAID.[88]

A study published in *Nature* on April 30, 2015 revealed that single-dose attenuated Vesiculovax vaccines protect nonhuman primates against the new West African Makona variant of the Zaire ebolavirus.[89] Phase I clinical testing in human subjects was expected to commence in the second quarter of 2015 (although confirmation of the start is as yet unavailable).

MVA-BN Filo + AdVac

The MVA-BN Filo + AdVac prime-boost vaccine regimen combines AdVac technology from Janssen (Johnson & Johnson) and MVA-BN Filo technology from Bavarian Nordic. MVA-BN Filo contains the glycoproteins of the Ebola Zaire, Ebola Sudan, and Marburg viruses – and thus could have broad application. Research on this pathway, supported by a grant from the NIH, began in 2008.

Several safety and immunogenicity trials of MVA-BN Filo in prime-boost regimens with various adenovirus-based vaccines are currently underway:

a) A Phase I first-in-human study of heterologous prime-boost regimens using MVA-BN-Filo and Ad26.ZEBOV administered in different sequences and

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[85] Moynihan, M. "Profectus BioSciences Receives $8.6 Million HHS Contract to Accelerate Ebola Vaccine into Human Clinical Studies", *PR Newswire*, October 22, 2014, available at: http://www.prnewswire.com/news-releases/profectus-biosciences-receives-86-million-hhs-contract-to-accelerate-ebola-vaccine-into-human-clinical-studies-655290947.html.

[86] Profectus BioSciences Inc, Press Release, October 31, 2014, available at: http://www.profectusbiosciences.net/pdfs/releases/2014%201031%20Profectus%20DoD%20Tri-V%20Ebola%20Contract.pdf.

[87] Moynihan, M. "Profectus BioSciences' Ebola Vaccine Shown Effective and Safe in Providing Rapid, Single-Dose Protection Against Current "Makona" Ebola Outbreak Strain in Non-Human Primates", *PR Newswire*, April 8, 2015, available at: http://www.prnewswire.com/news-releases/profectus-biosciences-ebola-vaccine-shown-effective-and-safe-in-providing-rapid-single-dose-protection-against-current-makona-ebola-outbreak-strain-in-non-human-primates-300062931.html.

[88] Profectus BioSciences, VesiculoVax™ Prophylactic Vaccines for Public Health and Biodefense, available at: http://www.profectusbiosciences.net/pipeline/vesiculovax.html.

[89] See Mire, "Single-Dose Vesiculovax Vaccines."

schedules in healthy adults was launched in the United Kingdom in December 2014 and is expected to be completed by February 2016.[90]

b) A Phase I randomized, placebo-controlled, observer-blind study of heterologous and homologous prime-boost regimens using MVA-BN-Filo and Ad26.ZEBOV in healthy adults was launched in December 2014 in Maryland and is actively recruiting. The study is expected to be completed by March 2016.[91]

c) Another Phase I study of heterologous prime-boost regimens using MVA-BN-Filo and Ad26.ZEBOV was launched in March 2015 in Nairobi, Kenya and is actively recruiting participants in both Kenya and Ghana. The study is expected to be completed by July 2016.[92] A similar study is currently recruiting participants in Uganda and potentially Tanzania, with results also expected by July 2016.[93]

d) MVA-BN Filo has also been used as a booster in two Phase I studies of cAd3-EBOZ, the vaccine candidate (discussed above) being developed by GSK and NIAID.

- MVA-BN Filo was first used as a booster in October 2014 in a Phase Ib, dose-escalating safety and immunogenicity trial of the monovalent Ebola Zaire candidate vaccine, cAd3-EBO Z and the heterologous prime-boost candidate vaccine regimen of cAD3-EBO Z followed by MVA-BN Filo in adults aged 18-50 years. This was conducted in Bamako, Mali by the University of Maryland, the Wellcome Trust, the NIAID, and Leidos Biomedical Research, Inc. It is estimated to be completed by December 2015.[94]
- MVA-BN Filo was then used as a booster in a Phase Ia, dose-escalating, safety and immunogenicity trial of the monovalent Zaire Ebola viral vector candidate vaccine cAd3-EBO Z and the heterologous prime-boost candidate vaccine regimen cAd3-EBO Z and MVA-BN Filo in healthy adults in September 2014 in the United Kingdom. This study was set for completion by May 2015 but no results have yet been posted.[95]

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[90] ClinicalTrials.gov, "A Safety and Immunogenicity Study of Heterologous Prime-Boost Ebola Vaccine Regimens in Healthy Participants," #NCT02313077, available at: https://clinicaltrials.gov/ct2/show/results/NCT02313077?term=MVA-BN-Filo&rank=5.

[91] ClinicalTrials.gov, "A Safety and Immunogenicity Study of Heterologous and Homologous Prime-Boost Ebola Vaccine Regimens in Healthy Participants," # NCT02325050, available at: https://clinicaltrials.gov/ct2/show/study/NCT02325050?term=MVA-BN-Filo&rank=7.

[92] ClinicalTrials.gov, "A Study to Evaluate the Safety and Immunogenicity of Heterologous Prime-Boost Ebola Vaccine Regimens in Healthy Participants," # NCT02376426, available at: https://clinicaltrials.gov/ct2/show/study/NCT02376426?term=MVA-BN-Filo&rank=6.

[93] ClinicalTrials.gov, "A Study to Assess the Safety and Immunogenicity of Heterologous Prime-Boost Ebola Vaccine Regimens in Healthy Participants," # NCT02376400, available at: https://clinicaltrials.gov/ct2/show/results/NCT02376400?term=MVA-BN-Filo&rank=2.

[94] ClinicalTrials.gov, "Phase 1 Trial of Ebola Vaccine in Mali," # NCT02267109, available at: https://clinicaltrials.gov/ct2/show/study/NCT02267109?term=MVA-BN-Filo&rank=4.

[95] ClinicalTrials.gov, "A Study to Assess New Ebola Vaccines, cAd3-EBO Z and MVA-BN® Filo," # NCT02240875, available at: https://clinicaltrials.gov/ct2/show/NCT02240875?term=MVA-BN-Filo&rank=1.

e) In July 2015, a Phase II study of the prime-boost vaccine regimen using MVA-BN Filo and Ad26.ZEBOV was initiated in the United Kingdom and France as part of the collaborative EBOVAC2 project involving The University of Oxford, the French Institute of Health and Medical Research (Inserm), the London School of Hygiene & Tropical Medicine (LSHTM), La Centre Muraz (CM), Inserm Transfert (IT) and Janssen. The UK study site is led by the Oxford Vaccines Group; sites in France will be coordinated by Inserm. The study will involve a total of 612 healthy adult volunteers in both countries. A second Phase II study in 1,200 volunteers is set to take place in Africa in the third quarter of 2015.[96]

In October 2014, Bavarian Nordic entered into a global licensing and supply agreement for its MVA-BN Filo vaccine candidate with Crucell Holland B.V. (Janssen/Johnson & Johnson). Under the terms of the agreement, Bavarian Nordic will grant Janssen an exclusive license for the vaccine. Bavarian Nordic will receive an upfront payment of $25 million and is entitled to up to $20 million in development and regulatory milestones, as well as royalties for commercial sales outside of Africa. Janssen will bear all costs associated with the development and commercialization of the vaccine. In addition, Bavarian Nordic will expand its production to manufacture more than 1 million doses of the vaccine valued at $99.3 million. (Of that amount, Janssen will pay $70.8 million upfront and $28.5 million for deliveries in 2015.) Johnson & Johnson Development Corporation will also invest approximately $43 million to purchase new shares of Bavarian Nordic.[97]

In January 2015, Johnson & Johnson announced the formation of consortia with leading global research institutions and non-government organizations to work with Janssen to accelerate the development of this vaccine regimen. The Innovative Medicines Initiative (IMI) plans to award these consortia grants totaling more than €100 million to support vaccine development, manufacturing, and patient education. Organizations involved include the London School of Hygiene & Tropical Medicine, the University of Oxford, the Institut National de la Santé et de la Recherche Médicale (INSERM), La Centre Muraz, Bavarian Nordic A/S, Vibalogics, the Grameen Foundation, and World Vision of Ireland.[98]

In September 2014, January 2015, April 2015, and June 2015, Crucell Holland B.V. received funding of $8.1 million, $1.8 million, $1.7 million, and $7.4 million respectively, from the US Department of Health and Human Services (NIAID) for the advanced development of these vaccines. All four contracts are set for completion by January 2020.[99]

DPX-Ebola

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[96] Bavarian Nordic, Press Release, July 15, 2015, available at http://www.bavarian-nordic.com/investor/news/news.aspx?news=4491.

[97] Bavarian Nordic, Press Release, October 22, 2014, available at: http://id.bavarian-nordic.com/media/news.aspx?news=4241.

[98] "Johnson & Johnson Announces Formation of Ebola Vaccine Development Consortia, Gains Funding from Innovative Medicines Initiative," Press Release, January 16, 2015, available at: https://www.jnj.com/news/all/Johnson-Johnson-Announces-Formation-of-Ebola-Vaccine-Development-Consortia-Gains-Funding-from-Innovative-Medicines-Initiative.

[99] The details of this contract (#HHSN272200800056C) are available at www.usaspending.gov (last visited 25 June 2015).

Immunovaccine, a company based in Nova Scotia, developed its DPX-Ebola vaccine using its DepoVax platform technology and Ebola antigens provided by NIH/NIAID. The results of a study conducted by NIAID published in August 2014 revealed that all animal subjects vaccinated with DPX-Ebola survived exposure to a lethal dose of the Ebola Zaire virus. Immunovaccine is currently working with NIH/NIAID to conduct further animal studies of the vaccine platform.[100]

Novavax Ebola GP Vaccine

Maryland-based Novavax has developed an Ebola virus glycoprotein (GP) recombinant nanoparticle vaccine candidate that targets the Makona variant of the Zaire Ebola virus. Only a low dose is required to produce an effective immune response due to the combined use of an adjuvant called Matrix-M. The dose-sparing and enhanced antibody effect of the addition of the Matrix-M adjuvant,[101] combined with Novavax's capacity to produce millions of doses per month, makes this candidate especially promising.[102]

In March 2015, Novavax presented data from a second non-human primate study conducted by the NIH/NIAID Division of Microbiology and Infectious Diseases (NIH-NIAID-DMID). In that study, animals received two injections of a 5μg dose of Novavax's vaccine together with its Matrix-M adjuvant and were then given a lethal dose of the Ebola virus. The control animals died, whereas the vaccinated animals remained healthy 18 days later.[103]

Novavax is currently conducting in Australia a Phase I clinical trial of this combination candidate. The trial is a randomized, observer-blinded, dose-ranging study to evaluate the safety and immunogenicity of the vaccine, with and without Matrix-M adjuvant, in 230 healthy adult subjects aged between 18 and 50 years. Although the primary goal is an evaluation of safety in this population, the study will also evaluate immunogenicity as measured by concentrations of serum IgG antibodies to the Makona strain glycoprotein.[104]

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[100] See M. Terry & R. McDermid, "Ebola Clinical Trials: Big Name Players In The Ebola Race," *BioSpace*, October 20, 2014, available at: http://www.biospace.com/News/ebola-clinical-trials-big-name-players-in-the/350579#sthash.DyvUOJLt.dpuf.

[101] Novavax, Press Release, "Novavax announces initiation of Ebola vaccine Phase I clinical trial supported by non-human primate challenge data and documented rapid manufacturing capabilities," February 12, 2015, available at: http://ir.novavax.com/phoenix.zhtml?c=71178&p=irol-newsArticle&ID=2016192.

[102] Idrus, A. "Novavax's Ebola vaccine is in hot pursuit of GSK, Merck, J&J candidates," *FierceVaccines*, February 18, 2015, available at: http://www.fiercevaccines.com/story/novavaxs-ebola-vaccine-hot-pursuit-gsk-merck-jj-candidates/2015-02-18.

[103] Novavax, Inc., "Novavax Presents New Data From Non-Human Primate Ebola Challenge at the 7th International Symposium on Filoviruses," March 28, 2015, available at: http://globenewswire.com/news-release/2015/03/28/719860/10126772/en/Novavax-Presents-New-Data-From-Non-Human-Primate-Ebola-Challenge-at-the-7th-International-Symposium-on-Filoviruses.html.

[104] Novavax, "Novavax Announces Initiation of Ebola Vaccine Phase I Clinical Trial Supported by Non-Human Primate Challenge Data and Documented Rapid Manufacturing Capabilities," Press Release, 12 February 2015, available at: http://ir.novavax.com/phoenix.zhtml?c=71178&p=irol-newsArticle&ID=2016192.

The study is expected to be completed by April 2016.[105] Initial data from the study showed that the vaccine was well-tolerated, elicited strong antibody responses and resulted in significant antigen dose-sparing when used in conjunction with the Matrix-M adjuvant.[106]

VXA ZEBOV GP

California-based Vaxart Inc. has developed an Ebola vaccine in tablet form that can be shipped and stored without refrigeration, potentially increasing the effectiveness of large-scale immunization campaigns in areas with limited cold-chain infrastructure.[107] Self-administration by tablet also reduces the need for healthcare personnel and injection equipment. Vaxart's vaccine delivery platform consists of a vector-adjuvant combination that can be used with any recombinant antigen.[108]

In a preclinical study conducted at the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) in 2014, Vaxart's vaccine candidate demonstrated protective efficacy against the Ebola virus. In October 2014, Vaxart announced that it would be accelerating its Ebola tablet vaccine program, with human clinical trials expected to commence in the first quarter of 2015.[109]

In January 2015, Vaxart raised $18.4 million through a convertible-note financing round led by Care Capital, its lead investor and largest shareholder. The additional capital will allow Vaxart to expand its clinical pipeline significantly, including the performance of Phase I trials of its Ebola vaccine in early 2015.[110] To date, no information regarding the initiation of these trials has been published.

Rabies Vector Vaccine

Researchers from NIAID and Thomas Jefferson University in Philadelphia have developed a vaccine candidate that combines the EBOV glycoprotein (GP) with an inactivated version of the rabies virus (RABV). Following successful studies of the RABV/EBOV vaccine in mice, studies were conducted of its safety, immunogenicity, and protective efficacy in non-human primates. In a study partially funded by the NIAID,

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[105] ClinicalTrials.gov, "Study to Evaluate the Immunogenicity and Safety of an Ebola Virus (EBOV) Glycoprotein (GP) Vaccine in Healthy Subjects," #NCT02370589, available at: https://clinicaltrials.gov/ct2/show/NCT02370589?term=novavax&rank=8.

[106] Novavax, Press Release, "Novavax Announces Positive Top-Line Data from Phase 1 Ebola Vaccine Trial on WHO Teleconference", July 21, 2015, available at http://novavax.com/download/files/news/Novavax_Announces_Postive_Ebola%20Data_at_WHO_Update_FINAL.pdf.

[107] BusinessWire, "Vaxart Completes Financing to Fund Expanding Development Portfolio", January 8, 2015, available at: http://www.businesswire.com/news/home/20150108005268/en/Vaxart-Completes-Financing-Fund-Expanding-Development-Portfolio#.VZDPpF6WGbA

[108] Vaxart, Official website, available at: http://www.vaxart.com/TechPlatformScience.html.

[109] Reuters, "Vaxart Accelerates Development of Ebola Tablet Vaccine", 23 October 2014, available at http://www.reuters.com/article/2014/10/23/ca-vaxart-idUSnBw235315a+100+BSW20141023.

[110] BusinessWire, "Vaxart Completes Financing to Fund Expanding Development Portfolio", January 8, 2015, available at: http://www.businesswire.com/news/home/20150108005268/en/Vaxart-Completes-Financing-Fund-Expanding-Development-Portfolio#.VZDPpF6WGbA

researchers tested three variants of the vaccine in fifteen rhesus macaques and found that they induced an immune response sufficient to offer protection from lethal EBOV infection.[111]

Among the advantages of this candidate is that it would provide protection against both Ebola and rabies. Rabies remains a serious threat to public health in Africa, claiming an estimated 24,000 lives per year. Therefore, a bivalent vaccine conferring protection from both viruses may be an efficient public-health tool.[112]

The RABV/EBOV vaccine was recently improved by increasing the expression of EBOV GP using codon-optimization. The new vaccine was successfully tested in four nonhuman primates with 100% protection against lethal EBOV challenge.[113]

In October 2014, the RABV/EBOV vaccine was exclusively licensed by NIAID to Minnesota-based Exxell BIO, which expects to test and commercialize it.[114] Phase I clinical trials are expected to commence in early 2015. To date, no information regarding the commencement of these trials has been published.

Inovio Ebola Vaccine

Pennsylvania-based Inovio Pharmaceuticals has developed yet another promising Ebola vaccine. Preclinical testing of the candidate protected 100% of vaccinated guinea pigs and mice from death after exposure to the virus.[115] In September 2014, Inovio announced that, in the first half of 2015, it would collaborate with GeneOne Life Science, Inc., in a Phase I clinical trial of the candidate. If it's successful, the companies will jointly seek additional resources to develop and commercialize the product.[116]

In April 2015, Inovio announced that it had been selected by the Defense Advanced Research Projects Agency (DARPA) to lead a $45 million program to expedite the development of novel products to prevent and treat Ebola. The other collaborators in the program are MedImmune (AstraZeneca), GeneOne Life Sciences and its subsidiary VGXI, Inc., Professor David B. Weiner of The Perelman School of Medicine at the University of Pennsylvania, Emory University, and Vanderbilt University. The Inovio-led consortium is developing and testing the following products:

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111 See J. Blaney, "Antibody Quality and Protection from Lethal Ebola Virus Challenge in Nonhuman Primates Immunized with Rabies Virus Based Bivalent Vaccine," *PLOS Pathogens* 9, no. 5 (2013).

112 See ibid.

113 See M. Willet, "Preclinical Development of Inactivated Rabies Virus–Based Polyvalent Vaccine against Rabies and Filoviruses," *Journal of Infectious Diseases Advance Access* (2015).

114 NIH, "NIH Grants License Agreement for Candidate Ebola Vaccines," Media Release, October 15, 2014, available at: http://www.niaid.nih.gov/news/newsreleases/2014/Pages/EbolaVaxLicense.aspx.

115 Inovio, "Inovio Pharmaceuticals Ebola Vaccine Moving into Human Trial with GeneOne Life Science", News Release, 24 September 2014, available at: http://ir.inovio.com/news/news-releases/news-releases-details/2014/Inovio-Pharmaceuticals-Ebola-Vaccine-Moving-into-Human-Trial-with-GeneOne-Life-Science/default.aspx.

116 Ibid.

a) a therapeutic DNA-based monoclonal antibody product (dMAb), which could be designed and manufactured expediently on a large scale using common fermentation technology, is thermal-stable, and may provide more rapid therapeutic benefit than other vaccine candidates.
b) a potent conventional protein-based therapeutic monoclonal antibody product (mAb), which could be administered either just before or just after exposure to Ebola virus. (Unlike vaccines, immunoprophylaxis by mAbs does not develop long-term immune memory. Therefore its immediate protection would need to be supplemented by a vaccine for longer-term protection.)
c) Inovio's DNA-based vaccine against Ebola, with the first patient expected to be tested in the second quarter of 2015.[117]

The collaboration will cover pre-clinical development costs for the dMAb products and mAb candidates, GMP manufacturing costs, and Phase I clinical trials. MedImmune will manufacture the protein mAbs, while the Inovio-GeneOne/VGXI team manufactures the DNA-based products. The funding period is two years with a base award of $21 million and an optional award of $24 million. There is also an option of $11 million (contingent upon the successful completion of certain pre-clinical development milestones) to support additional product-supply and clinical-development activities. The consortium has adopted an unusually aggressive development timeline, pursuing the three projects discussed above in parallel.[118]

In May 2015, Inovio announced that it had initiated a Phase I trial of its products. Five groups of healthy subjects will receive Inovio's Ebola immunotherapy (INO-4212) and its components (INO-4201 and INO-4202), alone or in combination with INO-9012, using Inovio's DNA delivery technology.[119]

Protein Sciences Corporation BEVS Technology

In December 2014, Meriden-based Protein Sciences Corporation shipped its Ebola vaccine candidate to an NIH facility in Maryland for animal testing.[120] The candidate was derived using the same Baculovirus Expression Vector System (BEVS) platform that is used to manufacture influenza vaccines. If the tests are successful, the NIH may fund further development and production.[121] The results of the study have not yet been published.

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[117] Inovio, Press Release, April 8, 2015, available at: http://ir.inovio.com/news/news-releases/news-releases-details/2015/Inovio-Pharmaceuticals-Selected-by-DARPA-to-Lead-a-45-Million-Program-to-Expedite-Development-of-Novel-Products-to-Prevent-and-Treat-Disease-Caused-by-Ebola/default.aspx.

[118] Ibid.

[119] Inovio Pharmaceuticals, "Inovio Initiates Clinical Trial With DNA Immunotherapies to Prevent and Treat Ebola", May 12, 2015, available at: http://ir.inovio.com/news/news-releases/news-releases-details/2015/Inovio-Initiates-Clinical-Trial-With-DNA-Immunotherapies-to-Prevent-and-Treat-Ebola/default.aspx.

[120] Skahill, P. "Connecticut Company Ships Ebola Vaccine to NIH for Testing", *WNPR*, December 19, 2014, available at: http://wnpr.org/post/connecticut-company-ships-ebola-vaccine-nih-testing#stream/0.

[121] Dowling, B. "Protein Sciences Expects To Begin Testing Ebola Vaccine", *Hartford Courant*, October 6, 2014, available at: http://www.courant.com/business/hc-ebola-vaccine-meriden-protein-sciences-20141006-story.html.

GOVX-E301 and GOVX-E302

Georgia-based GeoVax Labs, Inc. is developing two Ebola vaccines, GOVX-E301 and GOVX-E302. Both are recombinant MVA (Modified Vaccinia Ankara) vaccines based on an attenuated smallpox virus. GOVX-E301 is designed for use against the Zaire strain of Ebola in epidemic conditions, whereas GOVX-E302 is designed for routine immunization against the three most lethal strains of Ebola: Zaire, Sudan, and Bundibugyo. GeoVax will be collaborating with the US Centers for Disease Control (CDC) in Atlanta and using their BSL-4 facilities for testing. GeoVax is accelerating its program with the objective of producing the monovalent GOVX-E301 vaccine by 2016.[122]

In April 2015, GeoVax announced that it had entered into a Research Collaboration Agreement with NIAID to accelerate the development of vaccines against filoviruses including Ebola and Marburg. NIAID will contribute materials, reagents, scientific advice, and data analysis; GeoVax will construct and characterize MVA-Ebola and MVA-Marburg recombinants in vitro and prepare MVA Ebola and Marburg vaccines for animal studies, which will be conducted by NIAID.[123]

In May 2015, GeoVax announced the commencement of preclinical animal studies in NIH's BSL-4 facilities. Initial results are promising and are expected to be released at the end of the summer.[124] The company intends to begin testing in non-human primates in late 2015 and to advance to human clinical trials by late 2016 or early 2017.[125]

Triazoverin

Russian scientists at the Ural branch of the Russian Academy of Sciences, in collaboration with specialists from the Health Ministry's Institute for Influenza Studies and Ural University, have developed an experimental Ebola vaccine called Triazoverin (or Triazaverine).[126] The vaccine is reported to have demonstrated efficacy of 70 – 90% against hemorrhagic fever viruses such as Marburg, but it has not yet been tested on the Ebola virus, and its chemical composition has not been publicly revealed.[127] At a meeting with WHO Director-General Margaret Chan in October 2014, Russian President Vladimir Putin offered

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[122] GeoVax, Recent News, "GeoVax Announces Initiation of Ebola Vaccine Development Program", October 2, 2014, available at: http://www.geovax.com/news-events/entry/2014/10/02/geovax-announces-initiation-of-ebola-vaccine-development-program.html.

[123] GeoVax, Recent News, "GeoVax Enters Into Research Collaboration Agreement with the NIH for Ebola/Marburg Vaccines", April 16, 2015, available at: http://www.geovax.com/news-events/entry/2015/04/16/geovax-enters-into-research-collaboration-agreement-with-the-nih-for-ebola-marburg-vaccines.html.

[124] GeoVax, Recent News, "GeoVax Reports 2015 Second Quarter Financial Results and Provides Corporate Update", August 10, 2015, available at http://www.geovax.com/news-events/entry/2015/08/10/geovax-reports-2015-second-quarter-financial-results-and-provides-corporate-update.html.

[125] GeoVax, Recent News, "GeoVax Reports 2015 First Quarter Financial Results And Provides Corporate Update", May 13, 2015, available at: http://www.geovax.com/news-events/entry/2015/05/13/geovax-reports-2015-first-quarter-financial-results-and-provide-corporate-update.html.

[126] TASS, "Ebola vaccine produced at two laboratories in Russia", October 13, 2014, available at: http://tass.ru/en/russia/754070.

[127] See A. Rivas, "Russia Says It Has an Ebola Vaccine; but with the Time It Takes to Test, It Could Be Too Little Too Late," *Medical Daily*, October 14, 2014.

to send shipments of Triazaverine to West Africa to help curb the epidemic.[128] The Russian government intends to ship the experimental vaccine to Guinea for initial testing in nonhuman primates.[129] Russia also claims to have developed two additional Ebola vaccines, the details of which have not been publicly released.[130] Clinical testing of at least one vaccine candidate is set to occur in August 2015.[131]

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The table on the following page summarizes these 12 projects.

[128] See J. Corsi, "Putin offers WHO experimental Ebola vaccine," *WND,* October 14, 2014, available at: http://www.wnd.com/2014/10/putin-offers-who-experimental-ebola-vaccine/.

[129] See Rivas, "Russia Says It Has an Ebola Vaccine."

[130] BBC News, "Ebola treatments – how far off?", October 14, 2014, available at: http://www.bbc.com/news/health-29613902.

[131] Interfax, "Novosibirsk virologists to submit Ebola vaccine for clinical tests in August", *Russia Beyond the Headlines,* June 4, 2015, available at http://rbth.com/news/2015/06/04/novosibirsk_virologists_to_submit_ebola_vaccine_for_clinical_tests_in_au_46630.html.

	Candidate	Developer	Supplementary Funding or Assistance	Testing Stage
1.	VSV-EBOV	New Link Genetics/ Merck	HHS/BARDA ($30 million)	I, II, and III
2.	cAd3-EBO-Z	GSK/NIH/NIAID	Wellcome Trust/Medical Research Council/DFID (share of $4.6 million); Bill & Melinda Gates Foundation ($3 million); BARDA ($12.9 million); European Commission ($19.8 million); Swiss Government ($1.98 million)	I, II and III
3.	VesiculoVax	Profectus BioSciences Inc./Galveston National Laboratory	NIAID ($5.4 million); NIAID (share of $26 million); DOD/JVAP ($8.5 million); BARDA ($5.8 million); DoD ($9.5 million)	Preclinical
4.	MVA-BN Filo + AdVac	Crucell Holland B.V./Janssen (Johnson & Johnson)/Bavarian Nordic	Innovative Medicines Initiative (share of €100 million); NIAID ($11.6 million)	I, II
5.	DPX-Ebola	Immunovaccine	NIAID	Preclinical
6.	Ebola GP Vaccine	Novavax	NIAID	I
7.	VXA ZEBOV GP	Vaxart Inc.	N/A	Preclinical
8.	Rabies Vector Vaccine	NIAID/Thomas Jefferson University/ IDT Biologika	NIAID	Preclinical
9.	DNA-based monoclonal antibody product dMAb	Inovio Pharmaceuticals	DARPA (share of $45 million)	I
10.	BEVS platform	Protein Sciences Corporation	N/A	Preclinical
11.	GOVX-E301 and GOVX-E302	GeoVax Labs, Inc.	N/A	Preclinical
12.	Triazoverin/ Triazaverine	Russian Academy of Sciences	N/A	Preclinical

Antiviral Therapies

Until a vaccine emerges from this pack and is administered to all persons at risk of exposure to the Ebola virus, a therapy that would cure infected persons – or at least enable them to survive – will remain highly useful. Since the onset of the West African Outbreak, nine projects seeking to develop such a therapy have commenced or accelerated.

ZMapp

San Diego-based Mapp Biopharmaceutical (Mapp) has produced highly promising antiviral drug, known as ZMapp, for the treatment of Ebola.[132] ZMapp consists of a cocktail of highly purified monoclonal antibodies, optimized from two previous antibody cocktails. It was derived, in January 2014, from Ebola antibody research supported by the Canadian and U.S. governments and Defyrus, Inc., a Toronto-based life sciences and biodefense company.[133]

Since 2011, Gary Kobinger has led research at the Public Health Agency of Canada's National Microbiology Laboratory in Winnipeg aimed at generating antibodies that could prevent Ebola infections in monkeys and stall its advancement after infection. The fruits of this research were combined with an antibody developed by Mapp to create a new antibody cocktail that demonstrated greater efficacy in non-human primates. Other drugs already tested in monkeys had to be given within 24 hours of infection, whereas the new cocktail, ZMapp, displayed 100% effectiveness when given up to five days after infection.[134] Indeed, ZMapp was able to reverse Ebola symptoms (including elevated liver enzymes, mucosal haemorrhages, and generalized petechial), leading to full recovery of all treated animals by 28 days post-infection.[135]

In March 2014, the NIH awarded a five-year $28 million grant to establish a consortium to identify and develop antibodies to fight the Ebola virus.[136] The project includes researchers from 15 institutions including Mapp, which received $1.2 million from the NIH for its role in the Consortium for Immunotherapeutics Against Viral Hemorrhagic Fevers.[137]

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[132] One indication of the hopes that are pinned on this project is that ZMapp has already been administered under emergency protocols to nine Ebola victims, including the first two U.S. medical missionaries in Liberia who were infected in July 2014. Kent Brantly, MD, and Nancy Writebol were the first two Ebola victims who were successfully treated on U.S. soil. See D. Kroll, "Zmapp Ebola Trial Starts in Liberia: Is It Too Late?," *Forbes*, March 1, 2015.

[133] See ibid.

[134] See ibid.

[135] See X. Qiu, "Reversion of Advanced Ebola Virus Disease in Nonhuman Primates with Zmapp," *Nature* 514 (2014).

[136] Bigelow, B. "Mapp Bio's Ebola Drug Shows Promise, But Making More Will Take Time," *Xconomy*, August 15, 2014, available at: http://www.xconomy.com/san-diego/2014/08/15/mapp-bios-ebola-drug-shows-promise-but-making-more-will-take-time/.

[137] See https://www.usaspending.gov/transparency/Pages/TransactionDetails.aspx?RecordID=3A92C497-F4C7-496B-9E8F-F8D9F61104B8&AwardID=28877664&AwardType=SG.

In September 2014, LeafBio/Mapp received a $25 million grant from BARDA to develop, manufacture, and test ZMapp. In addition to funding, BARDA will provide expertise and technical support for manufacturing, regulatory, and nonclinical activities. BARDA can extend the contract up to a total of $42.3 million. Mapp will manufacture a small amount of the drug for early-stage clinical safety studies and nonclinical studies to assess the drug's safety and efficacy in humans. Mapp will also work with BARDA to increase production yields and ramp up the scale of manufacturing.[138]

In March 2015, the NIAID announced the launch of a multicenter Phase I/II study of ZMapp in Liberia, Sierra Leone and the United States. The study is expected to be completed by December 2016.[139] Infected patients in both control and ZMapp groups will receive the same standard of patient care: intravenous fluids, balancing electrolytes, maintaining oxygen status and blood pressure, and treating other infections if they occur.[140]

Meanwhile, NIAID is also conducting a Phase Ia open-label study to assess the safety and pharmacokinetics of administration of a single dose of ZMapp to healthy adult volunteers. The study is being conducted in Maryland and is expected to be completed by May 2016. It is currently recruiting participants.[141]

TKM-Ebola

Vancouver-based Tekmira Pharmaceuticals has developed an anti-viral therapy known as TKM-Ebola, which harnesses ribonucleuic acid interference (RNAi) to combat the virus. It attempts to block particular genes of the virus and thereby to inhibit its replication.

In May 2010, preclinical studies conducted by Tekmira, in collaboration with researchers from Boston University and the United States Army Medical Research Institute for Infectious Diseases (USAMRIID), demonstrated the capacity of the drug to protect nonhuman primates, previously infected with the Zaire Ebola virus, from the disease.[142] Soon thereafter, Tekmira was awarded a substantial grant by the U.S. Department of Defense (DoD). The grant contemplated that Tekmira would receive $34.7 million over the course of three years, during which it would test the drug on animals and conduct the first

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[138] HHS, "HHS contracts with Mapp Biopharmaceutical to develop Ebola drug", September 2, 2014, available at: http://www.hhs.gov/news/press/2014pres/09/20140902b.html.

[139] ClinicalTrials.gov, "Putative Investigational Therapeutics in the Treatment of Patients With Known Ebola Infection", # NCT02363322, available at: https://clinicaltrials.gov/ct2/show/NCT02363322?term=zmapp&rank=1.

[140] See Kroll, "Zmapp Ebola Trial Starts."

[141] ClinicalTrials.gov, "Safety and Pharmacokinetics of a Single ZMappTM Administration in Healthy Adult Volunteers", # NCT02389192, available at: https://clinicaltrials.gov/ct2/show/NCT02389192?term=zmapp&rank=2.

[142] Tekmira, "TKM-Ebola and TKM-Ebola_Guinea," available at http://www.tekmira.com/portfolio/tkm-ebola.php (last visited June 29, 2015). These studies were funded in part by the U.S. Department of Defense's Joint Project Manager Transformational Medical Technologies (JPM-TMT) Office. Ibid.

round of safety testing on humans. The DoD would then have the option to contribute $105 million more to finance further development and testing to obtain FDA approval.[143]

Initially, this collaboration went swimmingly, and several other organizations signed on. In 2013, the DoD funded the development of new formulations of the drug.[144] Soon threafter, the FDA granted TKM-Ebola a "fast-track" designation, raising the possibility that, while its safety must be demonstrated through human trials, its efficacy might be established through animal studies. In the first half of 2014, Tekmira conducted a randomized, single-blind, placebo-controlled single-ascending-dose Phase I clinical trial evaluating TKM-Ebola in healthy volunteers. Before commencing a similar study involving multiple ascending doses, the company has been obliged to provide the FDA additional data related to the mechanism of cytokine release and to modify the test protocol to ensure patient safety.[145]

Meanwhile, the company developed a modified version of its therapeutic, known as TKM-Ebola-Guinea, which targets the Makona strain of Ebola that caused the West African Outbreak.[146] Preclinical studies of the new version showed sufficient promise that Tekmira entered into a Manufacturing and Clinical Trial Agreement with the University of Oxford to provide TKM-Ebola-Guinea for a Phase II clinical study in West Africa.[147] That trial began in March of 2015. High hopes for TKM-Ebola-Guinea prompted many organizations to lend it their financial or administrative support. In addition to Oxford University, they included the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), the Wellcome Trust, the Sierra Leone College of Medicine and Allied Health Sciences, the Sierra Leone Ministry for Health, the WHO-based Special Programme for Research and Training in Tropical Diseases (TDR), the UK Department for International Development (DFID), Public Health England, and GOAL Global.[148] Unfortunately, the initial fruits of the trial were not encouraging. On June 19, 2015 the company announced that enrollment for the trial had closed, because "continuing enrollment was not likely to demonstrate an overall therapeutic benefit."[149] On July 20, 2015, Tekmira announced the suspension of its TKM-Ebola program and added that it would be re-evaluating its development contract with the Department of Defense. The company plans to re-brand

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143 Timmerman, L. "Tekmira nails $140M defense contract to make RNAiD drug for Ebola", *xconomy*, July 15, 2010, available at: http://www.xconomy.com/seattle/2010/07/15/tekmira-nails-140m-defense-contract-to-make-rnai-drug-for-ebola/.

144 Tekmira, "TKM-Ebola & TKM-Ebola-Guinea."

145 Ibid.

146 See AFP, "Ebola test drug cures infected monkeys," *New Vision*, April 23, 2015, available at: http://www.newvision.co.ug/news/667354-ebola-test-drug-cures-infected-monkeys.html; Tekmira, Press Release, "Tekmira Provides Update on TKM-Ebola-Guinea", June 19, 2015, available at: http://investor.tekmirapharm.com/releasedetail.cfm?ReleaseID=918694.

147 Tekmira, "TKM-Ebola & TKM-Ebola-Guinea.

148 Wellcome Trust, "New Trial of TKM-Ebola treatment to start in Sierra Leone," March 11, 2015, available at: http://www.wellcome.ac.uk/News/Media-office/Press-releases/2015/WTP058880.htm (last visited June 29, 2015).

149 Tekmira, Press Release, "Tekmira Provides Update on TKM-Ebola-Guinea", June 19, 2015, available at: http://investor.tekmirapharm.com/releasedetail.cfm?ReleaseID=918694 (last visited June 29, 2015).

itself as "Arbutus Biopharma Corp." and to focus exclusively on its Hepatitis B drug development program.[150]

BCX4430

BCX4430 is a viral RNA-dependent RNA polymerase (RdRp) inhibitor developed by North Carolina-based BioCryst Pharmaceuticals in collaboration with the NIAID. Like TKM-Ebola, it functions by inhibiting viral replication long enough to enable activation of the body's natural immune system. BioCryst did not initially set out to develop an Ebola drug. Instead it, like several other companies, was trying to develop a cure for Hepatitis C. When BCX4430 showed only modest ability to suppress replication of the Hepatitis C virus, the company's scientists tested it on other viruses – and discovered its efficacy in slowing replication of filoviruses, among which are Ebola and Marburg.[151]

In September 2013, the NIAID awarded BioCryst a five-year contract to fund the development and initial testing of the drug. Animal studies followed quickly, and in December of 2014, the company began a Phase I clinical trial, using healthy volunteers.[152] Subsequently, the NIAID exercised additional options under the contract, raising the total amount of funding to almost $30 million.[153] In March 2015, BioCryst received another round of funding, similar in amount, from BARDA, which should enable the company to scale up manufacturing enough to support additional clinical trials.[154]

So far, indications of efficacy have been strong. In preclinical studies, BCX4430 effectively shielded rodents from Ebola and Marburg viruses, and macaques from Marburg virus, even when it was administered as late as 48 hours after infection.[155] A Phase I double-blind, placebo-controlled, dose-ranging study to evaluate the safety, tolerability, and pharmacokinetics of BCX4430 administered via intramuscular injection in healthy subjects is currently ongoing and recruiting participants in the United Kingdom. The study is being run by BioCryst and NIAID and is expected to be completed by August 2015.[156]

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[150] CBC News, "Tekmira to suspend Ebola drug development, focus on hepatitis B", July 20, 2015, available at http://www.cbc.ca/news/health/tekmira-to-suspend-ebola-drug-development-focus-on-hepatitis-b-1.3159858.

[151] See Frank Vinluan, "Biocryst Bets on New Ebola Drug to Fight Bioterror, Outbreak Threats," *Exome* (2014).

[152] See ClinicalTrials.gov, "A Phase 1 Study to Evaluate the Safety, Tolerability and Pharmacokinetics of BCX4430", # NCT02319772, available at: https://clinicaltrials.gov/ct2/show/results/NCT02319772?term=BCX4430&rank=1.

[153] BioCryst Pharmaceuticals, Press Release, "BioCryst Awarded BCX4430 Advanced Development Contract", available at: http://investor.shareholder.com/biocryst/releasedetail.cfm?ReleaseID=904146 (last visited June 29, 2015); BioCryst Pharmaceuticals, Press Release, "BioCryst Receives Additional NIAID Funding for Manufacture and Development of BCX4430 to Treat Hemorrhagic Virus Diseases", available at: http://investor.shareholder.com/biocryst/releasedetail.cfm?ReleaseID=871598 (last visited June 29, 2015).

[154] BioCryst Pharmaceuticals, Press Release, "BioCryst Awarded BCX4430 Advanced Development Contract", March 31, 2015. Available at: http://investor.shareholder.com/biocryst/releasedetail.cfm?ReleaseID=904146.

[155] See T. Warren, "Protection against Filovirus Diseases by a Novel Broad-Spectrum Nucleoside Analogue Bcx4430," *Nature* 508 (2014).

[156] ClinicalTrials.gov, "A Phase 1 Study to Evaluate the Safety, Tolerability and Pharmacokinetics of BCX4430", # NCT02319772, available at: https://clinicaltrials.gov/ct2/show/results/NCT02319772?term=BCX4430&rank=1.

BioCryst CEO Jon Stonehouse has said that BioCryst "has no intention of making money off of viral outbreaks in Africa." If BCX4430 wins FDA approval and is then stockpiled by the U.S. government as a bioterror countermeasure, Stonehouse promises to donate its remaining stores of the drug to fight future outbreaks in poor countries. "If we get a stockpiling order, we've achieved our business goal," he has indicated. "So then it's doing what's right, which is to make it available to these places that can't afford it."[157]

Favipiravir

Favipiravir is a broad-spectrum antiviral drug developed by Toyama Chemical Co. Ltd, a unit of Fujifilm Holdings Corp. In March 2012, Toyama's U.S. partner, Boston-based Medivector Inc., received a $138.5 million contract from the Department of Defense's Joint Project Manager Transformation Medical Technologies (JPM-TMT) initiative to further develop favipiravir as a broad-spectrum therapeutic against multiple influenza viruses.[158] Then, in November 2014, with the West African Outbreak well underway, the Department of Defense awarded Medivector a $30 million cost-plus-incentive-fee contract for Phase II clinical trials of favipiravir as an anti-viral treatment for Ebola. The tests will be performed in Boston and in Africa. Fiscal 2015 research, development, testing, and evaluation funds in the amount of $7.9 million are being obligated at the time of the award; the Army Contracting Command, Natick, Massachusetts, is the contracting activity.[159]

For several reasons, this drug could be highly beneficial. In 2014, two independent studies in mice infected with Ebola virus showed that the administration of 150 mg/kg of favipiravir twice a day within 6 days of infection induced rapid virus clearance, reduced biochemical parameters of disease severity, and produced 100% survival.[160] Favipiravir has also shown anti-Ebola efficacy in immunodeficient murine models; has shown good tolerance in thousands of adult humans in anti-influenza trials; has been approved for treating novel or resistant influenza infections in Japan; is immediately available; can be administered orally to both adults and children; and has been approved for compassionate use by the French drug safety agency ANSM.[161] Furthermore, the oral nature of administration offers patients the opportunity to interrupt treatment if needed.[162]

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[157] See Vinluan, "Biocryst Bets on New Ebola Drug."

[158] Genetic Engineering & Biotechnology News, "DoD Awards MediVector $138.5M for Broad Spectrum Flu Therapeutic," March 16, 2012, available at: http://www.genengnews.com/gen-news-highlights/dod-awards-medivector-138-5m-for-broad-spectrum-flu-therapeutic/81246504/.

[159] Global Biodefense, "Army Awards 30M to MediVector for Ebola Drug," November 18, 2014, available at: http://globalbiodefense.com/2014/11/18/army-awards-30m-medivector-ebola-drug/.

[160] See F. Mentré, "Dose Regimen of Favipiravir for Ebola Virus Disease," *The Lancet* (2014).

[161] ClinicalTrials.gov, "Efficacy of Favipiravir Against Ebola (JIKI)", #NCT02329054, available at: https://clinicaltrials.gov/ct2/show/NCT02329054?term=favipiravir&rank=5.

[162] Van Herp, M. et al. "Favipiravir – a prophylactic treatment for Ebola contacts?", *The Lancet*, June 13, 2015, available at http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(15)61095-9.pdf.

A Phase II efficacy study on Favipiravir is currently underway in Guinea. The study is expected to be completed by September 2015.[163] Preliminary data show that favipiravir is not effective in individuals who already display very high levels of viral replication with serious visceral involvement, but demonstrates greater efficacy in individuals with a high or moderate level of viral replication, who have not yet developed severe visceral lesions.[164] The trial, sponsored by Inserm and funded by the European Commission from the Horizon 2020 Initiative (under the project title REACTION), is supported by Médecins Sans Frontières (MSF), the Alliance for International Medical Action (ALIMA), the Belgian First Aid and Support Team (B-FAST), the European Mobile Laboratory (EMLab), the French Red Cross, and the French Military Health Service.[165]

AVI-7537

AVI-7537 is an anti-viral drug developed by Cambridge-based Sarepta Therapeutics to treat Ebola virus. It is a Phosphorodiamidate Morpholino Oligomer that binds directly to the viral VP24 transcript RNA to prevent Ebola viral replication.[166] The drug functions by interfering with RNA-signaling involved in protein synthesis in order to alter the molecular structure of viral bodies and thus slow or halt the progression of disease.[167]

In 2010, Sarepta (then AVI Biopharma) received a $291 million contract from the Department of Defense for the research and development of treatments for both the Ebola and Marburg viruses.[168] The contract initially provided Sapreta with $80 million and was intended to be extended three more times if the firm achieved certain technical milestones. In 2012, however, the Department of Defense issued a stop order due to lack of government funding, and Sapreta lost half of its contract (approximately $145 million) that had been intended for Ebola research.[169]

Preclinical studies have demonstrated the efficacy of AVI-7537 in treating Ebola virus in nonhuman primates, diminishing multiple aspects of viral-induced pathology in test subjects.[170] In November 2014, the results of two Phase I clinical studies were published, demonstrating no clinical or toxicologic safety concerns with AVI-7537.[171] Results of a

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163 Ibid.

164 MSF, "Preliminary results of the JIKI clinical trial to test the efficacy of favipiravir in reducing mortality in individuals infected by Ebola virus in Guinea", February 24, 2014, available at: http://www.msf.org/article/preliminary-results-jiki-clinical-trial-test-efficacy-favipiravir-reducing-mortality.

165 Ibid.

166 See P. Iversen, "Discovery and Early Development of Avi-7537 and Avi-7288 for the Treatment of Ebola Virus and Marburg Virus Infections," *Viruses* 4, no. 11 (2012).

167 ECRI Institute, "AVI 6002 (AVI-7537) Drug Therapy (Sarepta Therapeutics) for Treating Ebola Virus Disease", 18 November 2014, available at: https://www.ecri.org/components/ProductBriefs/Pages/14371.aspx.

168 G. Bernard, "Sarepta's AVI-7537: Hope for an Ebola Cure is Rekindled in Cambridge," *BostInno*, 6 August 2014, available at: http://bostinno.streetwise.co/2014/08/06/sareptas-avi-7537-hope-for-an-ebola-cure-is-rekindled-in-cambridge/.

169 Ibid.

170 See Iversen, "Discovery and Development of Avi-7537 and Avi-7288."

171 See A. Heald, "Safety and Pharmacokinetic Profiles of Phosphorodiamidate Morpholino Oligomers with Activity against Ebola Virus and Marburg Virus: Results of Two Single-Ascending-Dose Studies," *Antimicrobial*

study conducted with the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) published in February 2015 showed that administration of AVI-7537 to rhesus monkeys infected with Ebola led to a 75% survival rate.[172] No further clinical studies are currently ongoing.

Alferon and Ampligen

Alferon is the only natural-source, multi-species alpha interferon currently approved for sale in the United States for the treatment of refractory or recurring external genital warts caused by human papilloma virus. Ampligen is an experimental class of RNA compounds being developed for debilitating diseases and disorders of the immune system, including chronic fatigue syndrome.[173] Both products have been developed by Philadelphia-based Hemispherx Biopharma, Inc.

In September 2014, Hemispherx and USAMRIID announced their collaboration in studying Alferon and Ampligen for the treatment of Ebola virus at USAMRIID's laboratories in Maryland.[174] Three reports lent support to this line of research:

- In December 2014, Hemispherx announced that it had received a report from researchers at Howard University, describing a study in which Ampligen strongly inhibited the Ebola minigenome in the human embryonic kidney cell system.
- Previously, a report from the University of Cagliari, Italy had shown that Ampligen can successfully bind to the lethal Ebola virus protein VP35, which inactivates a patient's immune system, leading to high morbidity and death rates.
- A report from USAMRIID scientists described the protective activity of both Alferon and Ampligen against the Ebola virus at low concentrations.[175]

Together, these reports have encouraged Hemispherx to accelerate clinical development of Ampligen for the prevention and treatment of Ebola.[176]

In May 2015, Hemispherx's European subsidiary, Hemispherx Biopharma Europe N.V./S.A., received formal notification from the European Commission approving its Orphan Medicinal Product Application for Ampligen to treat Ebola virus. Orphan drug

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Agents and Chemotherapy 58, no. 11. The study was conducted under contract with the Joint Product Management Office of BioDefense Therapeutics (BD-Tx). See Sarepta Therapeutics, Press Release, October 16, 2014, available at: http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irol-newsArticle&ID=1978732.

172 Warren, T. et al. "A Single Phosphorodiamidate Morpholino Oligomer Targeting VP24 Protects Rhesus Monkeys against Lethal Ebola Virus Infection," *mBio*, vol. 6 (1), February 2015.

173 Hemispherx Biopharma, Press Release, September 8, 2014, available at: http://www.hemispherx.net/content/investor/default.asp?goto=796.

174 Ibid.

175 Hemispherx Biopharma, Press Release, November 3, 2014, available at: http://www.hemispherx.net/content/investor/default.asp?goto=805.

176 Hemispherx Biopharma, Press Release, December 9, 2014, available at: http://www.hemispherx.net/content/investor/default.asp?goto=809.

designation promotes the clinical development of drugs that target rare life-threatening conditions and are expected to provide significant therapeutic advantage over existing treatments. The benefits of achieving orphan drug designation include eligibility for grants from the European Union and Member State programs as well as initiatives supporting research and development. The EU orphan drug designation is a preliminary step toward commercial approval; clinical testing is required before approval can be given.[177]

NanoViricides

In 2008 and 2009, Connecticut-based NanoViricides, a nanomedicine[178] company focused on anti-viral drugs, developed anti-Ebola drug candidates that demonstrated potential based on cell-culture and animal testing conducted by USAMRIID. However, the company de-emphasized this research initiative in order to focus on the development of its lead drug candidate for influenza. In September 2014, when the West African Outbreak was at its peak, NanoViricides restarted its anti-Ebola/Marburg drug program.[179]

NanoViricides has now developed additional novel drug candidates against Ebola that could potentially lead to a successful therapeutic.[180] In January 2015, the company shipped several such candidates to a high-security bio-containment facility in the U.S. for preliminary evaluation. NanoViricides has said that it possesses the capacity to produce sufficient quantities of a successful anti-Ebola drug in its new facility in Shelton, Connecticut, to combat the current Ebola epidemic.[181]

Hyperimmune horse serum (FBH-004)

In February 2015, the French biopharmaceutical company Fab'entech launched production of its Ebola treatment, FBH-004, which is a passive immunotherapy treatment based on the administration of highly purified fragments of specific equine polyclonal immunoglobulins.[182] The development of FBH-004 is currently at the stage of in-vitro proof of concept.[183] It will eventually enter clinical trials, with accelerated timing in order to meet the demands of the public health emergency in West Africa. The project is operated under the aegis of the WHO and supported by the European Medicines Agency (EMA), within

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[177] Hemispherx Biopharma, Press Release, May 11, 2015, available at: http://www.hemispherx.net/content/investor/default.asp?goto=824.

[178] A nanoviricide drug is made up of two components that are chemically connected: a virus-binding ligand that mimics the native receptor on the host cell to which the virus binds; and a backbone polymer that makes the nanoviricide resemble the host cell surface to the virus.

[179] NanoViricides, Press Release, September 9, 2014, available at: http://www.nanoviricides.com/press%20releases/2014/NanoViricides%20Reports%20That%20It%20Has%20Designed%20and%20Commenced%20Synthesis%20of%20Novel%20Ebola%20Drug%20Candidates.html.

[180] Ibid.

[181] PRNewswire, "NanoViricides Reports That It Has Shipped anti-Ebola Drug Candidates For Testing to a BSL-4 Hi-Security Biocontainment Laboratory", *Providence Journal*, January 22, 2015, available at: http://www.providencejournal.com/article/20150122/NEWS/301229900.

[182] See Fab'entech, Press Release, February 2015, available at: http://www.fabentech.com/actualite/info-press-uk/press-release-launching-ebola-treatment-feb-2015/; Fab'entech, Specific Polyclonal Antibodies, available at: http://www.fabentech.com/products/ebola-fbh-002-uk/.

[183] See Fab'entech, Pipeline, available at http://www.fabentech.com/products/pipeline-2/.

which a working group was established in the summer of 2014 to review all efficacy, safety and quality data available on experimental Ebola medicines.[184]

JK- 05

In August 2014, Beijing-based Sihuan Pharmaceutical Holdings Group Co. Ltd (Sihuan) announced that its Ebola drug candidate, "JK-05," had been successfully evaluated by health experts at the People's Liberation Army General Medical Department and was now approved as a special drug to meet military needs. The drug has been described as a small molecular chemical entity and a new RNA polymerase selective inhibitor. Although preclinical research has been completed and JK-05 has passed the broad spectrum of antiviral clinical safety evaluations, the drug is as yet only available to treat Ebola infections in emergency situations.[185]

JK-05 was originally developed by the Chinese Academy of Military Medical Sciences (AMMS) and was purchased by Sihuan in October 2014. Sihuan intends to collaborate with the Academy to develop the drug further.[186] In October 2014, Sihuan sent several thousand doses of its drug JK-05 to Africa for use by Chinese aid workers and also intends to conduct clinical trials there.[187]

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[184] Ibid.

[185] Sihuan Pharmaceuticals, Press Release, 29 August 2014, available at: http://www.sihuanpharm.com/index.php?a=show&m=Article&id=644&l=en.

[186] See P. Waldmeir and L. Hornby, "Chinese Company Develops Ebola Treatment," *Financial Times*, October 9, 2014.

[187] BioSpace, "Sihuan Pharmaceutical Sends Ebola Drug JK-05 To Africa, Eyes Clinical Trials", 18 October 2015, available at: http://www.biospace.com/News/sihuan-pharmaceutical-sends-ebola-drug-jk-05-to/350561

The following table summarizes these 9 projects.

	Candidate	**Developer**	**Supplementary Funding**	**Testing Stage**
1.	ZMAPP	Mapp Biopharmaceutical	NIH ($1.2 million); BARDA ($25 million)	I and II
2.	TKM-Ebola	Tekmira Pharmaceuticals	DoD ($140 million)	I and II
3.	BCX4430	BioCryst Pharmaceuticals/NIAID	NIAID ($29.1 million); BARDA ($35 million)	I
4.	Favipiravir	Toyama Chemical Co. Ltd/Medivector Inc.	DoD ($30 million); JPM-TMT ($138.5 million)	I and II
5.	AVI-7537	Sarepta Therapeutics	DoD ($80 million)	I
6.	Alferon and Ampligen	Hemispherx Biopharma/ USAMRIID	N/A	Preclinical
7.	Nanoviricide Ebola drug	NanoViricides	N/A	Preclinical
8.	FBH-004	Fab'entech	N/A	Preclinical
9.	JK-05	Sihuan Pharmaceutical Holdings Group Co. Ltd	N/A	Preclinical

References

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

Blaney, J. "Antibody Quality and Protection from Lethal Ebola Virus Challenge in Nonhuman Primates Immunized with Rabies Virus Based Bivalent Vaccine." *PLOS Pathogens* 9, no. 5 (2013).

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

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

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

Grady, D. "Ebola Vaccine, Ready for Test, Sat on the Shelf." *New York Times*, October 23, 2014.

Heald, A. "Safety and Pharmacokinetic Profiles of Phosphorodiamidate Morpholino Oligomers with Activity against Ebola Virus and Marburg Virus: Results of Two Single-Ascending-Dose Studies." *Antimicrobial Agents and Chemotherapy* 58, no. 11 (November 2014).

Iversen, P. "Discovery and Early Development of Avi-7537 and Avi-7288 for the Treatment of Ebola Virus and Marburg Virus Infections." *Viruses* 4, no. 11 (2012): 2806-30.

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.

Kroll, D. "Zmapp Ebola Trial Starts in Liberia: Is It Too Late?" *Forbes*, March 1, 2015.

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

Marzi, A. "Vesicular Stomatitis Virus-Based Ebola Vaccines with Improved Cross-Protective Efficacy." *Journal of Infectious Diseases* 204, no. Supplement 3 (2011).

Mentré, F. "Dose Regimen of Favipiravir for Ebola Virus Disease." *The Lancet* (2014).

Mire, C. "Single-Dose Attenuated Vesiculovax Vaccines Protect Primates against Ebola Makona Virus." *Nature* 520 (April 30, 2015).

Qiu, X. "Reversion of Advanced Ebola Virus Disease in Nonhuman Primates with Zmapp." *Nature* 514 (2014).

Regules, J.A. "A Recombinant Vesicular Stomatitis Virus Ebola Vaccine – Preliminary Report." *New England Journal of Medicine* (April 1, 2015).

Rivas, A. "Russia Says It Has an Ebola Vaccine; but with the Time It Takes to Test, It Could Be Too Little Too Late." *Medical Daily*, October 14, 2014.

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).

Surowiecki, J. "Ebolanomics." *The New Yorker*, August 25, 2014.

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

Vinluan, Frank. "Biocryst Bets on New Ebola Drug to Fight Bioterror, Outbreak Threats." *Exome* (2014).

Waldmeir, P., and L. Hornby. "Chinese Company Develops Ebola Treatment." *Financial Times*, October 9, 2014.

Warren, T. "Protection against Filovirus Diseases by a Novel Broad-Spectrum Nucleoside Analogue Bcx4430." *Nature* 508 (2014).

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).

Willet, M. "Preclinical Development of Inactivated Rabies Virus–Based Polyvalent Vaccine against Rabies and Filoviruses." *Journal of Infectious Diseases Advance Access* (2015).