Learning from Ebola: 
How Drug-Development Policy Could Help Stop Outbreaks of Infectious Diseases

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Between 2013 and 2015, an outbreak of Ebola Hemorrhagic Fever killed more than 11,000 people and devastated three countries in western Africa. Preventing or limiting similar outbreaks in the future will require public-health initiatives of many sorts. This essay examines one such initiative that has thus far received little attention: modification of the policies used by governments and nongovernmental organizations to shape the development and distribution of pharmaceutical products aimed at infectious diseases.

Part I of the paper summarizes the epidemiology of Ebola and the history of the recent outbreak. Part II considers the potential role of vaccines and medicines in combating Ebola and why we have thus far failed to develop them. Part III describes the various research projects provoked by the recent outbreak. Part IV considers several ways in which our drug development policies might be altered – either fundamentally or incrementally – that could strengthen the portfolio of ongoing research projects and reduce the incidence or severity of similar outbreaks in the future.

I. Background

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).1 These symptoms typically first appear 8 to 10 days after exposure to the virus.2 If untreated, they usually result in death.

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1 An early draft of this paper 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.

2 William Hale Professor of Intellectual Property Law, Harvard University.

3 Summer Intern, Berkman Center for Internet & Society; MPP 2017 Candidate, Harvard Kennedy School of Government.


6 to 9 days later. Infected pregnant women often suffer abortion, and infants born to mothers dying of infection typically are themselves infected.3

Key to the virulence of the virus is its surface glycoprotein (GP), which mediates viral entry into host cells.4 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 cytokines5 (also known as a cytokine storm or exaggerated inflammatory response), leading to intravascular coagulation, vascular collapse and multiple organ failure.6

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 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.7 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.8 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.9 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.10

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5 See Sullivan, "Ebola Virus Pathogenesis."


9 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.

## Ebola Outbreaks, 1976–present

<table>
<thead>
<tr>
<th>Location</th>
<th>Dates</th>
<th>Species</th>
<th>Cases</th>
<th>Deaths</th>
<th>Fatality Rate</th>
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<tr>
<td>1 Nzara, Sudan</td>
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<tr>
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<td>Sudan</td>
<td>34</td>
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</tr>
<tr>
<td>5 Taï National Park, Ivory Coast</td>
<td>1994</td>
<td>Taï Forest</td>
<td>1</td>
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<tr>
<td>6 Mékouka, Gabon</td>
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<td>Zaire</td>
<td>52</td>
<td>31</td>
<td>60%</td>
</tr>
<tr>
<td>7 Kikwit, Zaire</td>
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<td>315</td>
<td>254</td>
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<tr>
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<td>Zaire</td>
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<td>Zaire</td>
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<td>46</td>
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<tr>
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<td>200-2001</td>
<td>Sudan</td>
<td>425</td>
<td>224</td>
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<tr>
<td>11 Congo/Gabon border</td>
<td>2001-2005</td>
<td>Zaire</td>
<td>314</td>
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<tr>
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<td>13 Bamoukamba, Congo</td>
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<tr>
<td>14 Kabango, Uganda</td>
<td>2008</td>
<td>Bundibugyo</td>
<td>149</td>
<td>37</td>
<td>25%</td>
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<tr>
<td>15 Luebo, Congo</td>
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<td>Sudan</td>
<td>32</td>
<td>14</td>
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<tr>
<td>16 Nakisamata, Uganda</td>
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<td>Sudan</td>
<td>24</td>
<td>17</td>
<td>71%</td>
</tr>
<tr>
<td>17 Luwero, Uganda</td>
<td>2012</td>
<td>Sudan</td>
<td>7</td>
<td>4</td>
<td>57%</td>
</tr>
<tr>
<td>18 Isiro, Congo</td>
<td>2012</td>
<td>Bundibugyo</td>
<td>57</td>
<td>29</td>
<td>51%</td>
</tr>
<tr>
<td>19 Guinea; Sierra Leone; Liberia</td>
<td>2013-2015</td>
<td>Zaire (Makona strain)</td>
<td>28,490</td>
<td>11,312</td>
<td>40%</td>
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</tbody>
</table>

West Africa – Case Counts,” [http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html](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](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.
As the table suggests, several species of the Ebola virus have been identified, each of which has several distinct strains.¹¹ 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.¹² 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.¹³

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.¹⁴

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¹² See Wauquier, "Human Fatal Zaire Ebola Virus Infection."

¹³ See Sullivan, "Ebola Virus Pathogenesis."

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

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. Since then,

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16 Ibid.
however, small numbers of new cases have been reported in all three countries.\textsuperscript{20} 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.\textsuperscript{21} 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.\textsuperscript{22} 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.\textsuperscript{23} But we will not know for sure for another month.

\textit{II. The Potential Roles of Drugs}

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.\textsuperscript{24} Conditions were ripe for an “apocalyptic urban outbreak.”\textsuperscript{25} 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.\textsuperscript{26} 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.


\textsuperscript{22} 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.


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. 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.” 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. 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. In the United States, for example, combinations of medicines and vaccines made possible radical reductions in the incidence, mortality, and morbidity of almost all infectious diseases. The resultant health benefits are readily apparent from the following graph.

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29 This graph has been adapted from Gregory L. Armstrong, Laura A. Conn, and Robert W. Pinner, “Trends in Infectious Disease Mortality in the United States During the 20th Century,” Journal of the American Medical Association 281, no. 1 (1999). The only major infectious disease common in the United States for which we have thus far failed to develop a vaccine is HIV/AIDS. The persistence of AIDS, despite the gradual improvement of the therapies that mitigate it, accounts for the upward trend in the mortality rate after 1985. For additional detail concerning the roles of vaccines and medicines in fighting infectious diseases, see William Fisher & Talha Syed, Infection: The Health Crisis in the Developing World and What We Should Do About It (forthcoming, Stanford University Press; partial draft available at http://cyber.law.harvard.edu/people/tfisher/Infection.htm), Introduction.
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. 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 technologies. Others are much more hardy. An example of the latter is HIV. Despite enormous investments of effort and money, no effective vaccine for HIV has yet emerged from the labs. 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 that have been overcome.

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31 To date, more than 30 HIV vaccine projects have proceeded to clinical testing. Of those, four have completed efficacy trials. Only one has shown any significant power to prevent HIV infections in humans, and the effect of that single candidate (known as RV-144) was modest (31% efficacy in a small group of Thai volunteers). See WHO, “Global Update on the Health Sector Response to HIV, 2014,” pp. 22-23. Several circumstances, in combination, explain this disappointing result: the fact that, in the overwhelming majority of cases, HIV infection does not result in protective immunity, which deprives researchers of the naturally generated antibodies that are ordinarily employed to design vaccines; the extraordinary genetic diversity among HIV strains and the speed with which the virus evolves in vivo; and the difficulty of inducing immune protection in the mucosa, where the virus commonly enters the body. See David A. Garber, "Prospects for an Aids Vaccine: Three Big Questions, No Easy Answers," *The Lancet Infectious Diseases* 4
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.  

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 shown in Part I of this essay, 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 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. 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

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33 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
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. And it also explains why, they argue, few other research initiatives were launched prior to the latest outbreak.

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 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

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with one another informally and sometimes work closely together on individual projects (such as the GAVI Vaccine Alliance\(^36\)), 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\(^37\) 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. Many of the other infectious diseases that were then ravaging the developing world were sickening and killing vastly larger numbers. The relevant data (as of the eve of the West African Outbreak) are set forth in the table on the following page:\(^38\)


\(^{38}\) For the sources of these numbers, and summaries of the epidemiologies of the diseases, see Fisher & Syed, *Infection*, Introduction and Chapter 1.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Global Deaths (thousands)</th>
<th>Global DALYs $^{39}$ (thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV/AIDS</td>
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<tr>
<td>Tuberculosis</td>
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<td>1,355</td>
</tr>
<tr>
<td>Trichuriasis</td>
<td>0</td>
<td>666</td>
</tr>
<tr>
<td>Hookworm</td>
<td>0</td>
<td>3,246</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>5,764</strong></td>
<td><strong>388,410</strong></td>
</tr>
</tbody>
</table>

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

$^{39}$ The DALY metric, developed by the World Health Organization, is designed to measure the losses caused by a particular disease or condition both through premature deaths and through ill health. One DALY “can be thought of as one lost year of ‘healthy’ life.” See WORLD HEALTH ORGANIZATION, THE WORLD HEALTH REPORT at 137 (2003).
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.

III. The Current State of Ebola Drug Development

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 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*. 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.

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.

A. Vaccines

1. 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. During the next four years, representatives of

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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.
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 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

49 Ibid.
50 Ibid.
51 Ibid.
that the vaccine does not have to be kept frozen, making it easier to transport, store, and use in West Africa.\textsuperscript{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.\textsuperscript{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 limited.\textsuperscript{54} The vaccine has demonstrated efficacy in post-exposure treatment in nonhuman primate models\textsuperscript{55} when it is administered 30 minutes to 24 hours after infection.\textsuperscript{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:\textsuperscript{57}

\textbf{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.\textsuperscript{58} Initial results are promising.\textsuperscript{59}

\textbf{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.\textsuperscript{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.\textsuperscript{61}

\textbf{c)} Phase III efficacy study in Guinea (sponsored by the WHO, the Ministry of Health Guinea, Médecins Sans Frontières, Épicentre, and the Norwegian Institute of Public Health). Interim results of the trial became available at the end of July 2015 – and


\textsuperscript{54} See ibid.


\textsuperscript{56} See Regules, "Recombinant Vsv-Ebov."

\textsuperscript{57} See ibid.


\textsuperscript{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

are extremely promising.\textsuperscript{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.\textsuperscript{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.\textsuperscript{64}

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.\textsuperscript{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.\textsuperscript{66}

2. 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.\textsuperscript{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:


\textsuperscript{63} Ibid.

\textsuperscript{64} Global Biodefense, “100 Percent Efficacy Shown for VSV-EBOV Ebola Vaccine”, July 31, 2015, available at \url{http://globalbiodefense.com/2015/07/31/100-percent-efficacy-shown-for-vsv-ebov-ebola-vaccine/}

\textsuperscript{65} ClinicalTrials.gov, “Phase I Trial to Assess the Safety, Tolerability and Immunogenicity of an Ebola Virus Vaccine (VSV\textregistered G-ZEBOV)”, \# NCT02374385, available at: \url{https://clinicaltrials.gov/ct2/show/study/NCT02374385?term=VSV\%CE\%94G-ZEBOV&rank=1}.


\textsuperscript{67} See Ledgerwood, "Chimpanzee Adenovirus Vector Ebola Vaccine – Preliminary Report."
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); 59

d) A Phase I/1b, open-label, dose-escalation trial to evaluate the safety, tolerability and immunogenicity of cAd3-EBOZ in healthy adults aged 18-65 in the United States (estimated completion date: August 2016); 70 and

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


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.


74 Ibid.
In December 2014, BARDA awarded GSK a 31-month contract worth $12.9 million, with an option to raise the amount by $16,000.\textsuperscript{75} The money will be used to establish the initial material needed to start manufacturing the vaccine.\textsuperscript{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.\textsuperscript{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 project, the scale-up will be compressed to less than a year.\textsuperscript{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.\textsuperscript{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.\textsuperscript{80}

3. 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.\textsuperscript{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.\textsuperscript{82}

\textsuperscript{75} \textit{NewLink, GSK Get U.S. Funding for Faster Development of Ebola Vaccines}, \textit{REUTERS} (December 23, 2014), \url{http://www.reuters.com/article/2014/12/23/us-health-ebola-vaccine-idUSKBN0K11VW20141223}.

\textsuperscript{76} Ibid.


\textsuperscript{78} Ibid.

\textsuperscript{79} Ibid.

\textsuperscript{80} GlaxoSmithKline, “Forming public partnerships.”


\textsuperscript{82} Ibid.
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 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

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84 Ibid.


89 See Mire, "Single-Dose VesiculoVax Vaccines."
commence in the second quarter of 2015 (although confirmation of the start is as yet unavailable).

4. 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 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

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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

c) 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

5. DPX-Ebola

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

6. 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


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


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.\footnote{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: \url{http://ir.novavax.com/phoenix.zhtml?c=71178&p=irol-newsArticle&ID=2016192}.} The study is expected to be completed by April 2016.\footnote{ClinicalTrials.gov, “Study to Evaluate the Immunogenicity and Safety of an Ebola Virus (EBOV) Glycoprotein (GP) Vaccine in Healthy Subjects,” #NCT02370589, available at: \url{https://clinicaltrials.gov/ct2/show/NCT02370589?term=novavax&rank=8}.} 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.\footnote{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_Positive_Ebola%20Data_at_WHO_Update_FINAL.pdf.}

7. 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.\footnote{BusinessWire, “Vaxart Completes Financing to Fund Expanding Development Portfolio”, January 8, 2015, available at: \url{http://www.businesswire.com/news/home/20150108005268/en/Vaxart-Completes-Financing-Fund-Expanding-Development-Portfolio#VZDPfF6WGbA}.} 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.\footnote{Vaxart, Official website, available at: \url{http://www.vaxart.com/TechPlatformScience.html}.}

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.\footnote{Reuters, “Vaxart Accelerates Development of Ebola Tablet Vaccine”, 23 October 2014, available at \url{http://www.reuters.com/article/2014/10/23/ca-vaxart-idUSnBw235315a+100+BSW20141023}.}
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.\footnote{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#.VZDPpF6WGhA} To date, no information regarding the initiation of these trials has been published.

8. 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, 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.\footnote{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).}

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.\footnote{See ibid.}

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.\footnote{See M. Willet, "Preclinical Development of Inactivated Rabies Virus–Based Polyvalent Vaccine against Rabies and Filoviruses," Journal of Infections Diseases Advance Access (2015).}

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

9. Inovio Ebola Vaccine

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.  

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:

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.

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.

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.

\[116\] Ibid.  
\[118\] Ibid.  
In December 2014, Meriden-based Protein Sciences Corporation shipped its Ebola vaccine candidate to an NIH facility in Maryland for animal testing. 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. The results of the study have not yet been published.

11. 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.

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.

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

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end of the summer.\textsuperscript{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.\textsuperscript{125}

12. 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).\textsuperscript{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.\textsuperscript{127} At a meeting with WHO Director-General Margaret Chan in October 2014, Russian President Vladimir Putin offered to send shipments of Triazaverine to West Africa to help curb the epidemic.\textsuperscript{128} The Russian government intends to ship the experimental vaccine to Guinea for initial testing in nonhuman primates.\textsuperscript{129} Russia also claims to have developed two additional Ebola vaccines, the details of which have not been publicly released.\textsuperscript{130} Clinical testing of at least one vaccine candidate is set to occur in August 2015.\textsuperscript{131}

* * * * *

The table on the following page summarizes these 12 projects.


\textsuperscript{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.


\textsuperscript{129} See Rivas, "Russia Says It Has an Ebola Vaccine."


<table>
<thead>
<tr>
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<th>Developer</th>
<th>Supplementary Funding or Assistance</th>
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<td>New Link Genetics/ Merek</td>
<td>HHS/BARDA ($30 million)</td>
<td>I, II, and III</td>
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<tr>
<td>2. cAd3-EBO-Z</td>
<td>GSK/NIH/NIAID</td>
<td>Wellcome Trust/Medical Research Council/DFID (share of $4.6 million); Bill &amp; Melinda Gates Foundation ($3 million); BARDA ($12.9 million); European Commission ($19.8 million); Swiss Government ($1.98 million)</td>
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<tr>
<td>3. Vesiculovax</td>
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<tr>
<td>4. MVA-BN Filo + AdVac</td>
<td>Crucell Holland B.V./Janssen (Johnson &amp; Johnson)/Bavarian Nordic</td>
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<tr>
<td>5. DPX-Ebola</td>
<td>Immunovaccine</td>
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<td>6. Ebola GP Vaccine</td>
<td>Novavax</td>
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</tr>
<tr>
<td>7. VXA ZEBOV GP</td>
<td>Vaxart Inc.</td>
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<td>8. Rabies Vector Vaccine</td>
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<td>NIAID</td>
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<tr>
<td>9. DNA-based monoclonal antibody product dMAb</td>
<td>Inovio Pharmaceuticals</td>
<td>DARPA (share of $45 million)</td>
<td>I</td>
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<tr>
<td>10. BEVS platform</td>
<td>Protein Sciences Corporation</td>
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<tr>
<td>11. GOVX-E301 and GOVX-E302</td>
<td>GeoVax Labs, Inc.</td>
<td>N/A</td>
<td>Preclinical</td>
</tr>
<tr>
<td>12. Triazoverin/Triazaverine</td>
<td>Russian Academy of Sciences</td>
<td>N/A</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>
B. 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.

1. ZMapp

San Diego-based Mapp Biopharmaceutical (Mapp) has produced highly promising antiviral drug, known as ZMapp, for the treatment of Ebola.\(^\text{132}\) 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.\(^\text{133}\)

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.\(^\text{134}\) 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.\(^\text{135}\)

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.\(^\text{136}\) 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.\(^\text{137}\)

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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.


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

2. TKM-Ebola

Vancouver-based Tekmira Pharmaceuticals has developed an anti-viral therapy known as TKM-Ebola, which harnesses ribonucleic 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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140 See Kroll, "Zmapp Ebola Trial Starts."
Initially, this collaboration went swimmingly, and several other organizations signed on. In 2013, the DoD funded the development of new formulations of the drug.\footnote{Timmerman, L. “Tekmira nails $140M defense contract to make RNAiD drug for Ebola”, \textit{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/; Tekmira, “TKM-Ebola & TKM-Ebola-Guinea.”} Soon thereafter, 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.\footnote{Ibid.}

itself as “Arbutus Biopharma Corp.” and to focus exclusively on its Hepatitis B drug development program.\textsuperscript{150}

3. 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.\textsuperscript{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.\textsuperscript{152} Subsequently, the NIAID exercised additional options under the contract, raising the total amount of funding to almost $30 million.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{156}

\textsuperscript{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.”

4. 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. 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.

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. 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. Furthermore, the oral nature of administration offers patients the opportunity to interrupt treatment if needed.

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


A Phase II efficacy study on Favipiravir is currently underway in Guinea. The study is expected to be completed by September 2015. 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. 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.

5. 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. 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.

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. The contract initially provided Sarepta 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 Sarepta lost half of its contract (approximately $145 million) that had been intended for Ebola research.

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. In November 2014, the results of two Phase I clinical studies were published, demonstrating no clinical or toxicologic safety concerns with AVI-7537. Results of a study

163 Ibid.
165 Ibid.
169 Ibid.
170 See Iversen, "Discovery and Development of Avi-7537 and Avi-7288."
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.

6. 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


\(^ {174}\) Ibid.


7. NanoViricides

In 2008 and 2009, Connecticut-based NanoViricides, a nanomedicine 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.\textsuperscript{179}

NanoViricides has now developed additional novel drug candidates against Ebola that could potentially lead to a successful therapeutic.\textsuperscript{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.\textsuperscript{181}

8. 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.\textsuperscript{182} The development of FBH-004 is currently at the stage of in-vitro proof of concept.\textsuperscript{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


\textsuperscript{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.


\textsuperscript{180} Ibid.


\textsuperscript{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.\textsuperscript{184}

9. 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{187}

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\textsuperscript{184} Ibid.
The following table summarizes these 9 projects.

<table>
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<tr>
<th>Candidate</th>
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<th>Testing Stage</th>
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<tr>
<td>2. TKM-Ebola</td>
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<td>DoD ($140 million)</td>
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<td>3. BCX4430</td>
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<tr>
<td>5. AVI-7537</td>
<td>Sarepta Therapeutics</td>
<td>DoD ($80 million)</td>
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<td>6. Alferon and Ampligen</td>
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<td>7. Nanoviricide Ebola drug</td>
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<td>8. FBH-004</td>
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<tr>
<td>9. JK-05</td>
<td>Sihuan Pharmaceutical Holdings Group Co. Ltd</td>
<td>N/A</td>
<td>Preclinical</td>
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</tbody>
</table>
IV. Reform

The research projects described in the preceding section are likely soon to generate at least one safe and effective Ebola vaccine and at least one safe and effective Ebola therapy. Those drugs, in turn, will substantially strengthen our ability to respond to the next outbreak of the disease. However, four serious challenges remain.

First, the Ebola virus continues to evolve. Human-to-human transmission causes genomic drift, which is why the virus varies from outbreak to outbreak. The more people are infected, the faster the virus will mutate. A comparison of the genetic sequence of the Makona strain of the Zaire species of the virus (responsible for the 2014 outbreak) with the original strain of the Zaire species revealed 640 mutations – ten of which may affect the efficacy of three of the drugs currently in the developmental pipeline: ZMapp, TKM-Ebola, and AVI-7537. The mutations affect the parts of the virus that these drugs are specifically designed to interfere with or recognize, potentially affecting their ability to inhibit viral replication. The potential power of these drugs must now be re-evaluated against the current strain.

The mutability of the virus also means that the development of vaccines and drugs should not stop with the selection of those capable of suppressing the current versions of the disease. We must be ready, on short notice, to modify those products – or to replace them with wholly different products – when (not if) there is an outbreak based upon a new strain.

The second challenge is that we have no assurance that efficacious vaccines and therapies, when they finally do emerge, will be made available at affordable prices to the people, countries, and health organizations that need them. All of the drug candidates discussed above are – or likely will soon be – subject to patent protection. In addition, FDA and EMA approval, when they occur, will be accompanied by one or another form of data-exclusivity protection. The result is that, for the foreseeable future, the companies that have developed the drugs will be free to set the prices at which they are sold. To be sure, some countries (particularly in western Europe) will likely regulate the prices that the companies can charge. But this will not be the case everywhere.

Because the consumer demand curve may be sharply concave in certain markets with limited (or no) price controls, pharmaceutical companies with exclusive rights may follow a strategy of setting their prices at very high levels. This strategy is rational if the producer’s objective is to maximize profits. But it will deny access to the vaccines and drugs to large swaths of the population in dire need of them.

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The fact that the recipients of external funding might engage in behavior that might lead to a socially sub-optimal outcome may be surprising, insofar as most of the 21 ongoing projects have been funded, at least in part, either by a government agency and/or by a nonprofit foundation, which (one would expect) would want to maximize the social return on its investment. Haven’t the donors conditioned their grants upon commitments by the recipients to make the fruits of their ventures widely available, including for the world’s poor? In most cases, the answer appears to be no.

Agencies of the U.S. government are especially unlikely to include such conditions in their grants. To be sure, they typically do impose some obligations on grantees. For example:

- Most of such grants require the recipients to make publicly available some or all of the data and publications growing out of the funded research.¹⁹¹
- In addition, grants from US agencies (except for those under the Small Business Innovation Research program) commonly require recipients to give the US government royalty-free licenses to any patents that emerge from the funded projects.
- Funding from BARDA is typically accompanied by additional obligations – for examples, duties to deliver the products at issue to the federal government on specified terms.

However, US government grants typically do not prevent the recipients from patenting the drugs at issue or restrict the prices that the firms can charge parties other than the grantor.¹⁹² Nor does receipt of a voucher under the Adding Ebola to the FDA Priority

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¹⁹¹ The Standard Operating Procedures for the NIH include protocols for NIH grants and contracts. Applicants requesting $500,000 or more in direct costs for any year of a grant are required to share their data with the scientific community. NIH, Research Funding, available at: [http://www.niaid.nih.gov/researchfunding/sop/pages/datasharing.aspx](http://www.niaid.nih.gov/researchfunding/sop/pages/datasharing.aspx). In addition, NIH-funded researchers are required to submit final peer-reviewed manuscripts to a public archive of research publications (PubMed Central) and to show evidence of compliance with the public access policy in applications, proposals, and progress reports. NIH, Public Access of Publications SOP, available at: [http://www.niaid.nih.gov/researchfunding/sop/pages/publicaccess.aspx](http://www.niaid.nih.gov/researchfunding/sop/pages/publicaccess.aspx). Similarly, HHS Grants Policy requires that the results and accomplishments of HHS-funded activities should be made available to the public. PIs/PDs and recipient organizations are expected to make the results and accomplishments of their activities available to the research community and to the public at large. HHS Grants Policy Statement, page II-68, available at: [http://www.hhs.gov/asfr/ogapa/aboutog/hhsgps107.pdf](http://www.hhs.gov/asfr/ogapa/aboutog/hhsgps107.pdf). Special rules apply to applicants for Small Business Innovation Research (SBIR) Phase II funding of $500,000 or more of direct costs in any single year. If final data would not be amenable to sharing (e.g. proprietary data) the Small Business Concern (SBC) should explain this in the application. In addition, whether or not the award meets the threshold for data sharing, the Operating Division (OPDIV) will not release data outside the Federal government without the recipient’s permission for a period of 4 years from completion of the project under which the data were generated. HHS Grants Policy Statement, page II-127, available at: [http://www.hhs.gov/asfr/ogapa/aboutog/hhsgps107.pdf](http://www.hhs.gov/asfr/ogapa/aboutog/hhsgps107.pdf).

¹⁹² According to HHS Grants Policy, as long as recipients comply with the provisions of the Bayh-Dole Act, as amended by the Technology Transfer Commercialization Act of 2000 (P.L. 106-404), and 37 CFR part 401, they have the right to retain title to any invention conceived or first actually reduced to practice using HHS funds.

Some nongovernmental donors do impose more substantial restrictions on grantees. The pioneer in this regard has been the Gates Foundation. Its Global Access program, in force since 2003, “requires that (a) the knowledge and information gained from a Programmatic Investment be promptly and broadly disseminated, and (b) the Funded Developments be made available and accessible at an affordable price to our intended beneficiaries.”\footnote{“Bill & Melinda Gates Foundation Global Access Statement” (2015). Further information concerning the policy may be found at http://globalaccess.gatesfoundation.org.} In addition, the Foundation’s Open Access Policy requires the prompt and broad dissemination of all published research resulting from its funding.\footnote{The Foundation’s Open Access policy enables the unrestricted access and reuse of all peer-reviewed published research funded, in whole or in part, by the foundation, including any underlying data sets. As of January 1, 2015 the Foundation’s Open Access policy was effective for all new agreements. Bill & Melinda Gates Foundation, Open Access Policy, available at: http://www.gatesfoundation.org/how-we-work/general-information/open-access-policy.} But most funders seem not to have followed the lead of Gates.

The infrequency of assurances on this score may not prove to be disastrous. The companies that hold the intellectual-property rights to the drugs might decide not to enforce them. As indicated above, the CEO of BioCryst has already promised to make BCX4430 available on a no-profit basis in Africa if the drug receives FDA approval. Other firms developing vaccines or therapies may take similar stances. (It would not be surprising if they concluded that the public-relations benefits reaped by donating the drugs to African governments exceeded the maximum amount of the profits that could be secured by charging them monopoly prices.) But we have no assurance that they will. And the pricing practices adopted by most pharmaceutical firms in analogous circumstances in the past are not encouraging.

The third challenge is that our research funds are now most likely misaligned. Two years ago, the amount of resources committed to finding a vaccine or cure for Ebola were likely insufficient. Today, by contrast, 21 separate research projects, involving hundreds of millions of dollars, are underway. Whether that investment is excessive in an absolute sense would be difficult to say. But, at least if our goal is the maximization of global social welfare, we are almost certainly now concentrating too many resources on Ebola. Most of the afflictions catalogued in Part II of this essay consistently kill more people and cause more misery each year than Ebola has, even during the peak of the West African Outbreak. Yet, none of those diseases other than the “big three” (HIV, malaria, and TB) has attracted anywhere near as much research effort and funding as has, during the past year, Ebola.

Equally important, minimal resources are currently focused on finding vaccines or cures for Ebola’s cousins: other viral pathogens that could cause equally or even more
serious epidemics. These include the Marburg virus, the Machupo and Junin viruses (causes of the Bolivian and Argentinian hemorrhagic fevers, respectively); the Lassa virus (which continues to kill roughly 5000 people a year in west Africa); and the recently discovered Lloviu virus (which seems capable of survival among bats in Europe). As Bill Gates recently argued, we neglect such threats at our peril.

The fourth challenge is that the independence of the 21 projects surveyed in Part III is almost surely inefficient. Some degree of redundancy and autonomy among research ventures focused on a single medical target is sometimes beneficial; this is especially true in this particular context, because (as indicated above) the evolution of the Ebola virus means that the target is moving. But we have most likely exceeded the optimal level. Many of the projects involve the same biological mechanisms – and thus could benefit from the sharing of data. Some degree of such sharing is a byproduct of that fact that many of the research projects make use of a limited set of Biosafety Level 4 laboratories. But there could surely be more.

Addressing these four challenges is essential if we are to deploy an Ebola vaccine swiftly and effectively enough to prevent another devastating outbreak of the disease – and if we wish to prevent other, similar, or even more calamitous epidemics. So how might we do so? Subsection A, below, describes two alternative fundamental modifications of our drug-development policies, either of which would do the job. On the plausible assumption that fundamental reform is not yet on the horizon, subsection B considers some incremental adjustments of those policies that would at least help to address these four problems.

A. Fundamental Reform

The governments of most countries in the world attempt to manage the development and deployment of drugs in three ways: stimulating research and development; screening drugs for safety and efficacy; and ensuring that safe and efficacious drugs are made available to the people who need them. For simplicity, we will refer to these three dimensions as the incentive function, the regulatory function, and the access function.

You might expect that, in each country, a single government agency would conduct or coordinate the management of drugs. Remarkably, in no country is that true. Instead,

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199 We are grateful to Justin Hughes for making this point.

200 To be sure, coordination does have its hazards. In particular, it creates the risk that drug-approval decisions will be affected by considerations other than safety and efficacy. But those hazards can be minimized with appropriate safeguards against improper pressure on decision-makers. And the potential social benefits of greater coordination are huge.
the task is subdivided, and the separate dimensions are handled by different systems. In the United States, for example, the incentive function is performed by a combination of (a) government grants to universities and other parties engaged in research (totally roughly $30 billion per year) and (b) intellectual-property and data-exclusivity rights, which enable innovators to charge, for access to their products, prices much higher than the marginal costs of producing them. The regulatory function is performed through a system of “comprehensive licensure,” under which new pharmaceutical products may not be marketed in the United States unless and until they have been approved by the FDA. The access function is performed (highly imperfectly) by a combination of (a) direct and indirect subsidies for insurance and (b) antitrust law.

These are by no means the only ways in which the three functions might be fulfilled. Indicated in the following diagram are additional possible strategies – some of which are employed by other countries. (The circled phrases indicate the principal strategies used in the US.)

The particular combination of approaches used to manage drugs in the United States has many important strengths – and has helped make the US pharmaceutical industry the most innovative in the world. But it also has some well-known weaknesses. Most important, for present purposes, is that it rewards (and thus induces) a pattern of innovation that deviates in the following respects from the public interest:

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201 The following highly abbreviated summary of the systems currently employed in the United States is adapted from Fisher & Syed, Infection, Chapter 2 (preliminary draft available at http://cyber.law.harvard.edu/people/tfisher/Infection.htm).
1) Excessive investment in so-called “me-too drugs”;  
2) Insufficient investment in vaccines;  
3) A bias in favor of drugs that address late-stage cancers and against drugs that address early-stage cancers or would prevent cancer altogether;  
4) Insufficient investment in drugs aimed at diseases that affect the central nervous system;  
5) Insufficient investment in new diagnostic tests;  
6) Insufficient investment in diseases that primarily afflict the global poor.

Our collective failure, prior to 2013, to invest adequately in the development of an Ebola vaccine or drug is just one manifestation of the second and sixth of these distortions.

The most effective way of improving the manner in which we handle Ebola (and its cousins) would be to reform the systems we use to manage drugs in order to eliminate their systematic biases. At least two different reforms could work.

First, as several scholars have long argued, replacing or supplementing the patent and data-exclusivity systems on which we currently rely to stimulate research and development with a system in which drug developers are granted governmental prizes proportional to the health benefits of their innovations would go far toward eliminating all of the biases itemized above. Many varieties of prize systems have been proposed. The variant we prefer would have the following features:

- Prizes would initially be available only for pharmaceutical products (i.e., drugs and vaccines) that addressed neglected diseases, and then gradually

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expanded to pharmaceutical products addressing all other – global and non-neglected developing-region – diseases.

- Prize amounts would be calibrated so as to reward only the additional health benefits, measured in DALYs, offered by innovations over existing treatments.

- Prize recipients would be awarded, once a year for 10 years, a sum of money for each DALY saved anywhere in the world during the preceding year as a result of their innovations. The rate would initially be set at a low level, then gradually increased.

- The system would be optional, not mandatory or cumulative.

- The prize administrators would employ various tools to attract the right number of firms to therapeutic problems:
  o varying the amount of the prize offered;
  o offering prizes, not just to the winners of innovation races, but also to other contestants, provided that they finish within a prescribed period of time after the winners;
  o requiring firms considering applying for a prize to register both before they initiated a research project and before they commenced clinical trials; and
  o if necessary, capping the number of firms permitted to work simultaneously on a particular disease.

- Prize recipients would be required to waive their rights to enjoin follow-on innovation.

- The question of whether an improved drug built upon a pioneering drug, for which the pioneer has received a prize, would be resolved (imperfectly) by the courts, construing the pioneer’s patent. Upon a finding of infringement, the pioneer would require the follower to opt into the prize system. The pioneer would then be awarded a portion of the prize to which the follower would be entitled.

- The system would be created and implemented by a small consortium of developed countries.

Each of these specific suggestions is controversial, but this is not the right place to defend them. For present purposes, it suffices to observe that any one of various prize systems advocated by different groups of scholars would prompt pharmaceutical firms to redirect their R&D resources – away from “me-too drugs” and toward drugs that would prevent or ameliorate neglected diseases. Among the latter would be extremely hazardous viruses exemplified by Ebola.

Alternatively, instead of a prize system, we might supplement our current mechanisms for stimulating pharmaceutical innovation with a regulatory apparatus analogous to the one we employ in the United States to induce automobile manufacturers to increase the fuel efficiency of their fleets of vehicles. Under such a regime, all pharmaceutical firms would be required (as a condition of permission to sell their products in the United States) to
achieve each year a minimum social-responsibility index. The index would be a ratio, the numerator of which would consist of the aggregate health benefits (measured in DALYs) generated during the previous year through the distribution and consumption of the firm’s products, and the denominator of which would consist of the firm’s gross revenues (or some other measure of the firm’s income). Efficiency would be enhanced by permitting firms that are unable to fulfill this obligation to purchase DALY “credits” from other firms. (In other words, this would be a “floor-and-trade” approach.)

Such a regulatory regime would prompt firms to reorient either their internal R&D programs or their policies for acquiring the rights to drugs developed by other companies (or the companies themselves) in much the same way as would a prize system. It would differ from a prize system in two main ways. First, it would not require the expenditure of government resources. (To be sure, it would not be “free,” but its costs would be “off budget.”) Second, its moral valence would be different. Unlike a prize system, its adoption would convey the general message that pharmaceutical firms have moral obligations to deploy at least some of their resources in ways that benefit the global poor.

The details, merits, and limitations of these two approaches are examined in considerable detail in a forthcoming book by one of the co-authors of this article. Readers interested in pursuing them are encouraged to consult the draft. But, recognizing the barriers to implementation of these plans in the near term, we move on to more modest proposals.

B. Incremental Reform

Discussed below are four possible adjustments of the systems we currently employ to foster the development of vaccines and therapies and then make them publicly available. Any of these adjustments, we submit, would help us address the challenges set forth at the start of this Part.

1. Strings

As was noted in Part II, the global drug-development ecosystem contains many players other than national governments and pharmaceutical firms. A wide variety of public and private actors helps shape the portfolio of vaccines and therapies that we generate and the terms on which those products are marketed and distributed. One of the ways in which the various players interact is through donations – usually of money but sometimes of other services. The best known of those donations (mentioned several times already in this essay) are government grants to universities and pharmaceutical firms. But there are many more. The following chart attempts to map the most important.

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For present purposes, the most striking feature of this complex pattern of donations is how few of these donations come “with strings attached.” As indicated above, the grants that government agencies have recently made to the developers of Ebola drugs have been accompanied by very few conditions. Some nongovernmental foundations, led by Gates, do extract more substantial commitments from grantees. That strategy can and should be generalized and refined.

In the future, both government agencies and foundations, when giving money to researchers or manufacturers, should insist that they make their products available on socially beneficial terms. Among possible terms of this sort would be the following:

- **“No-profit, no-loss” pricing for the governments of low-income countries.** In other contexts, a few pharmaceutical firms have already agreed to make important therapies available to the governments of poor countries “at cost.” Sanofi, for example, has provided its anti-malarial drug ASAQ at “no-profit-no-loss” prices (less than US$0.50 for children under five year old and less than US$1 for older children and adults) to public organizations of endemic countries, international institutions, NGOs, and

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<tr>
<th>Donors</th>
<th>Developed-country gov’ts</th>
<th>Philanthropies</th>
<th>Banks</th>
<th>Universities</th>
<th>Pharma Firms</th>
<th>Scientists</th>
<th>Individuals</th>
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<tbody>
<tr>
<td><strong>Developing-country gov’ts</strong></td>
<td>Foreign Aid (e.g., PEPFAR; FDA services)</td>
<td>Bequests</td>
<td>Grants/low-interest loans; People</td>
<td>Expertise/Research/Licenses</td>
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<td>Grants</td>
<td>Bequests</td>
<td>Grants/low-interest loans</td>
<td>Expertise/Research/Licenses</td>
<td>Drugs; Compound Libraries</td>
<td>Expertise/time</td>
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<td>Legitimacy</td>
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<td><strong>Universities</strong></td>
<td>NIH Grants</td>
<td>Bequests</td>
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<td>Funding, compound libraries, info</td>
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<td>Grants</td>
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<tr>
<td><strong>Pharma Firms</strong></td>
<td>NIH Grants</td>
<td>CSR Funding</td>
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<td><strong>Hybrids</strong></td>
<td>Grants</td>
<td>Bequests</td>
<td>Grants/low-interest loans</td>
<td>Expertise; Licenses</td>
<td>Drugs</td>
<td>Time and effort</td>
<td>EML Access/Grants</td>
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<td><strong>Generic Firms</strong></td>
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<tr>
<td><strong>WHO/UN</strong></td>
<td>Funding</td>
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- a) **“No-profit, no-loss” pricing for the governments of low-income countries.** In other contexts, a few pharmaceutical firms have already agreed to make important therapies available to the governments of poor countries “at cost.” Sanofi, for example, has provided its anti-malarial drug ASAQ at “no-profit-no-loss” prices (less than US$0.50 for children under five year old and less than US$1 for older children and adults) to public organizations of endemic countries, international institutions, NGOs, and
programs promoting access to drugs in pharmacies.\textsuperscript{210} The recipients of grants for Ebola-related research could be required to adopt similar policies with respect to their discoveries. That would ensure that the public-health systems in poor countries are able to make the vaccines and therapies available to the populations that most need them.

b) \textit{Compulsory Licensing.} An alternative route to the same end would be to require grant recipients to issue to generic firms nonexclusive, royalty-free licenses to distribute the products in the poorest countries. Again, a policy recently adopted voluntarily by a pharmaceutical firm may provide a model: In 2014, Gilead Sciences, Inc. signed nonexclusive licensing agreements with seven Indian generic manufacturers to expand access to its Hepatitis C medicine, Sovaldi (sofosbuvir), in poor countries. The agreements permit the licensees to manufacture the drug for distribution in 91 developing countries, in which reside 54\% of the total global infected population. The licensees receive a complete technology transfer of the Gilead manufacturing process and set their own prices for the generic product, paying a modest royalty on sales to Gilead.\textsuperscript{211} Governments and NGOs funding Ebola research could require their grantees to make similar commitments. Ideally, the licenses that the grantees give to generic firms for Ebola vaccines and anti-viral therapies would be royalty-free, given the severity of the threat that the disease poses to the public health.

c) \textit{Mandatory differential pricing.} A plausible objection to the foregoing two proposals is that grant recipients must be able to recover their R\&D costs somehow; unless the size of the grants are increased sufficiently to fully offset those costs, the recipients must be able to make a profit by selling to someone. One way to address this objection would be to permit (but also compel) the firms to engage in differential pricing. For example, they might be forbidden to charge countries that the World Bank classifies as “low-income” more than enough to cover manufacturing costs, but allowed to charge “lower-middle-income” countries prices that generated a modest profit, “upper-middle-income” countries prices that generated a more substantial profit, and “high-income” countries whatever they wished.\textsuperscript{212} If the only countries interested in the vaccines and therapies were poor African countries, then this option would be no different from (a), above. But that appears not to be the case. The prospect of travelers


\textsuperscript{212} For lists of the countries in each category, see “World Development Indicators 2015”, available at: http://data.worldbank.org/products/wdi.
or health-care workers bringing the virus into wealthy countries is likely to prompt the governments thereof to purchase enough drugs to create stockpiles to meet future threats.\(^{213}\)

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\(d)\) \textbf{Data-sharing.} As indicated above, the recipients of Ebola-related grants are not currently obliged to share with other grant recipients data concerning the fruits of their research – at least until those projects are complete. They could be required to do so. At least some grant recipients would thus save money or time – and the public would be more likely to obtain life-saving drugs rapidly. Once again, a voluntary initiative is suggestive: In 2011, eight pharmaceutical firms (including Novartis, GlaxoSmithKline, AstraZeneca and Pfizer) joined a WIPO-led consortium to make “all available information on the subject of treating … neglected [tropical] diseases” available free of charge for the world’s least developed countries (LDCs). This initiative, known as WIPO Re:Search, has facilitated collaborations among researchers in hitherto isolated institutions.\(^{214}\) Grants to fund Ebola research could mandate similar practices.

Of course, not all potential grantees would be happy with conditions of these sorts. Some might credibly refuse to accept grants accompanied by such “strings.” To overcome their reluctance, the conditions might have to be tailored – or the amounts of the grants might have to be increased. In short, pursuit of this strategy would not be costless. But the social benefits could be very substantial.

2. Carrots

As we have seen, most of the 21 Ebola research projects currently underway have been funded, at least in part, by grants from government agencies and/or foundations. Such grants are, of course, discretionary. In other words, government or foundation decision-makers have assessed each of these projects and decided to fund them – and by how much. Presumably, they have decided not to fund other research proposals.

Decisions of this sort have a well-known limitation: Officials within the funding organizations typically know less than potential grantees concerning the merits and demerits of each grant proposal.\(^{215}\) As a result, they make mistakes – overfunding some weak projects and underfunding some strong ones.\(^{216}\) Prize systems – in which grantors offer rewards for

\(^{213}\) However, for the reasons explored in section IV.B.3., infra, the wealthy countries paying high prices might not include countries whose governments had contributed money to the research that led to the vaccine or drug at issue.


\(^{216}\) The most notorious example of poor decision-making in this regard is the failed effort of USAID to stimulate the development of a malaria vaccine. During the 1980s, the agency spent over $60 million on a project that, in its judgment, would likely lead to an effective vaccine. In the end, the initiative produced nothing of value. See Robert S. Desowitz, \textit{The Malaria Capers: Tales of Parasites and People} (New York: W.W. W.
successful completion of tasks – do not suffer from this difficulty. The superiority of prize systems in this regard helps to explain the support that many commentators have expressed for replacing the patent regime with a comprehensive prize system. As suggested above, such a radical change is not likely in the near future. But that does not mean that smaller-scale prizes could not be used to good effect to stimulate research on Ebola vaccines and drugs.

What might such targeted prizes look like? The simplest would be a commitment to pay a fixed amount of money to the first organization (presumably a pharmaceutical firm) to demonstrate (through specified forms of clinical testing) that it has created a vaccine capable of immunizing people against a particular strain of the Ebola virus. The recipient of the prize would be obliged to renounce patent and data-exclusivity protection – and to disclose publicly all information necessary to manufacture the vaccine.\(^\text{217}\) If the Ebola virus continues to evolve, a series of prizes might be employed to suppress each new strain. Many more complex variants of this general strategy are discussed in the extensive literature about prizes.

Included in the intricate set of laws (summarized in Section IV.A., above) employed in the United States to manage drugs are a few features that function as prizes – in particular, the priority-review voucher and the benefits accorded so-called “orphan drugs.” But these mechanisms are not well designed to concentrate research on the most promising and efficient potential projects. And, as we have seen, neither mechanism requires winners to forgo patent protection or to make their products available at affordable prices in developing countries. (Indeed, in the context of Ebola research, the orphan-drug regime may have perverse effects: The FDA’s designation of ZMapp as an orphan drug\(^\text{218}\) while eight other drugs sit in the pipeline has raised concerns that the market exclusivity obtained by the first-to-market will prevent subsequent candidates from launching, even if they are more effective. This would not only delay access to the most efficacious treatments but could disincentivize companies currently developing Ebola therapies.\(^\text{219}\))

The US government and/or the European Union could, at modest cost, implement a much more sensible and precise prize system focused on Ebola – or, perhaps a bit more broadly, on filoviridae. Alternatively (or in addition) the foundations that have been so critical to Ebola research could redirect some of the funds that they currently devote to grants.

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217 Norton, 1991). In truth, the probative value of this example is limited. The principal investigator, it turned out, was lining his own pockets, and the agency’s project director was receiving kickbacks. Thus, this particular episode may reveal more about the potential for a few corrupt actors to waste a great deal of money than it does about the merits of “push” programs in general.


Stockpiles and Strike Forces

One of the few conditions already contained in many of the Ebola-related grants is an obligation to permit the United States government to acquire (for free or on favorable terms) any drugs that issue from the research at issue. For example, in order to retain title to inventions produced with federal funds, recipients of NIH or HHS funding must formally grant the Federal government a limited-use license to the subject invention.\textsuperscript{220} Similarly, the Department of Defense requires that the US government shall, at a minimum, retain nonexclusive rights for the use of any inventions or patents resulting from federally funded research.\textsuperscript{221}

This convention raises the possibility of a strategy that could be implemented in the very near term. Most likely, the drafters of the contracts funding Ebola research contemplated that the U.S. government would exercise its rights by acquiring sufficient quantities of the drugs at issue to shield U.S. residents against the threats posed by infectious diseases – either from innocent travellers or from terrorists. But there is no reason why the same contractual rights could not be exercised by the government for broader purposes, including efforts beyond its own territory. Specifically, the United States government could acquire and stockpile sufficient quantities of the vaccines and drugs to enable them to be distributed extremely rapidly in regions where outbreaks occurred. Manufacturing significant quantities of a vaccine typically takes a substantial amount of time; a stockpile would enable deployment of the vaccine within days of the start of an outbreak.\textsuperscript{222} Such rapid strikes would prevent the virus from reaching U.S. shores – but it would also redound to the benefit of the residents of the countries in question. Stockpiles might also be deployed as foreign aid and/or humanitarian assistance.

Among its advantages, this approach would enhance substantially the power of the “strike forces” deployed by the United States to combat epidemics. In the late stages of the West African Outbreak, the United States sent teams of soldiers and physicians to Sierra Leone, Liberia, and Guinea to assist the overburdened public-health services there.\textsuperscript{223} That assistance would have been more effective if the teams had been able to bring with them larger supplies of drugs drawn from a pre-existing national stockpile.


\textsuperscript{222} Because most vaccines lose their effectiveness after some period of time, the stockpile would likely have to be “rolling.” Expired batches would have to be replaced periodically with new batches. This would of course increase the cost of maintaining such stockpiles.

Decisions concerning whether to draw down and then replenish stockpiles would be made from the standpoint of what would serve the national security and public health interests best, given the specific facts related to a particular outbreak. Just as the U.S. military makes decisions over where to deploy military hardware across the globe to best serve U.S. interests, so too would the government engage in a similar exercise here. A team of government officials would be charged with deciding how to deploy the stockpiled drugs and vaccines in areas around the globe, in conjunction with allies and multilateral agencies, to advance U.S. national security and public health interests. It need not wait until the virus infected US residents before deploying the stockpile in conjunction with a strike force.

4. Coordination

Part II suggested that one of the possible explanations for our collective failure, prior to 2013, to develop and test an Ebola vaccine is that the issue might have “slipped through the cracks.” Had there existed a single authority responsible for constantly assessing the relative magnitude of all threats to global health – and the relative costs of combating each one – this might not have happened. But no such authority stepped forward.

The World Health Organization (WHO) is mandated to “act as the directing and coordinating authority on international health work,”224 and to “establish and maintain effective collaboration with the United Nations, specialized agencies, governmental health administrations, professional groups, and such other organizations as may be deemed appropriate.”225 However, as the WHO itself acknowledges, its response to the 2014 Ebola outbreak failed to meet these responsibilities. Médecins Sans Frontières (MSF) has persuasively criticized the WHO for ignoring its early warnings about the unprecedented nature of the Ebola epidemic.226 MSF sounded the alarm as early as March 2014, calling for urgent action to halt the epidemic, but its calls were labeled unnecessary and alarmist.227 It was not until August 2014 that the WHO declared an international health emergency.228 The leaders of the WHO have themselves admitted that the organization was “too slow to see what was unfolding before us” and have since proposed a strengthened team of epidemiologists for detecting disease and a network of other providers to allow responders to reach “surge capacity.”229

Creating a new international authority responsible for public-health vigilance (or enhancing that ability of the WHO) would be a daunting task – one surely beyond the power of the United States acting alone. But a less ambitious response to this gap might be within

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225 Ibid.
227 In June 2014, MSF appealed to WHO’s Global Alert and Outbreak Response Network (GOARN) – a platform that pools technical and human resources in response to disease outbreaks – to deploy an effective response in West Africa, but its calls went largely unheeded. Ibid.
Suppose that one or more academic institutions (with no stake in developing responses to particular diseases) undertook to provide periodic assessments of the sort sketched above. Those assessments would be made available to the decision-makers in all of the public and private institutions that, collectively, are trying to address the global health crisis: governments, foundations, NGOs, and so forth. The assessments, by themselves, would of course not solve the problem; it would be essential that the various players then allocated among themselves responsibility for addressing each sector. But it would at least facilitate such coordination.

Among the potential benefits of this strategy would be a reduction in the “lumpiness” of public and private funding for research on infectious diseases. The surge in investment and effort provoked by the West African Outbreak of Ebola is commendable – and may well soon provide us with a much more robust quiver of weapons to combat the next appearance of this evolving disease.231 But all researchers involved in this field seem to agree that a steady stream of research and testing over a long period of time would have been both more efficient and more efficacious. Socially responsible choices concerning which diseases merit such sustained attention would be facilitated by a regularly updated map of the threats we collectively face and of the various ways in which each might be met.


231 Although almost 2,000 contacts remain under observation in Guinea and Sierra Leone, a small number of contacts in these countries have been lost to follow-up and are now untraceable. This includes a patient who disappeared in Guinea and may have infected other people as she crossed the border to visit a traditional healer. See Fox, M. “Ebola rates plummet, but WHO says more to come”, NBC News, August 5, 2015 available at http://www.nbcnews.com/storyline/ebola-virus-outbreak/ebola-rates-plummet-who-says-more-come-n404696.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad26.ZEBOV</td>
<td>Adenovirus Type-26 Vector-based Vaccine for Ebola Zaire virus</td>
</tr>
<tr>
<td>AdVac</td>
<td>Adenovirus vector technology</td>
</tr>
<tr>
<td>ALIMA</td>
<td>Alliance for International Medical Action</td>
</tr>
<tr>
<td>AMMS</td>
<td>Chinese Academy of Military Medical Sciences</td>
</tr>
<tr>
<td>ANSM</td>
<td>Agence Nationale de Sécurité du Médicament</td>
</tr>
<tr>
<td>AVI-7537</td>
<td>Anti-viral drug developed by Sarepta Therapeutics</td>
</tr>
<tr>
<td>B-FAST</td>
<td>Belgian First Aid and Support Team</td>
</tr>
<tr>
<td>BARDA</td>
<td>Biomedical Advanced Research and Development Authority</td>
</tr>
<tr>
<td>BCX4430</td>
<td>Anti-viral therapy developed by BioCryst Pharmaceuticals</td>
</tr>
<tr>
<td>BEVS</td>
<td>Baculovirus Expression Vector System</td>
</tr>
<tr>
<td>cAd3-EBO-Z</td>
<td>Ebola Zaire vaccine being developed by GlaxoSmithKline</td>
</tr>
<tr>
<td>CDC</td>
<td>US Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CIHR</td>
<td>Canadian Institutes of Health Research</td>
</tr>
<tr>
<td>DARPA</td>
<td>Defense Advanced Research Projects Agency</td>
</tr>
<tr>
<td>DFID</td>
<td>UK Department for International Development</td>
</tr>
<tr>
<td>dMAb</td>
<td>DNA-based monoclonal antibody product</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DoD</td>
<td>Department of Defense</td>
</tr>
<tr>
<td>DoD/JVAP</td>
<td>Department of Defense Joint Vaccine Acquisition Program</td>
</tr>
<tr>
<td>DPX-Ebola</td>
<td>Ebola vaccine being developed by Immunovaccine</td>
</tr>
<tr>
<td>EBOV</td>
<td>Ebola virus</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EMLab</td>
<td>European Mobile Laboratory</td>
</tr>
<tr>
<td>FBH-004</td>
<td>Hyperimmune horse serum being developed by Fab‟entech</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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</tr>
<tr>
<td>PREVAIL</td>
<td>Partnership for Research on Ebola Vaccines in Liberia</td>
</tr>
<tr>
<td>RABV</td>
<td>Rabies virus</td>
</tr>
<tr>
<td>RdRp</td>
<td>RNA-dependent RNA polymerase inhibitor</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>RNAi</td>
<td>Ribonucleic acid interference</td>
</tr>
<tr>
<td>rVSV</td>
<td>Recombinant vesicular stomatitis virus</td>
</tr>
<tr>
<td>STRIVE</td>
<td>Sierra Leone Trial to Introduce a Vaccine against Ebola</td>
</tr>
<tr>
<td>TDR</td>
<td>Special Programme for Research and Training in Tropical Diseases</td>
</tr>
<tr>
<td>TKM-Ebola</td>
<td>Anti-viral therapy being developed by Tekmira Pharmaceuticals</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
</tr>
<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
</tr>
<tr>
<td>USAMRIID</td>
<td>United States Army Medical Research Institute for Infectious Diseases</td>
</tr>
<tr>
<td>UTMB</td>
<td>University of Texas Medical Branch</td>
</tr>
<tr>
<td>VEBCON</td>
<td>VSV Ebola Consortium</td>
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<tr>
<td>VP24</td>
<td>Ebola virus protein</td>
</tr>
<tr>
<td>VP35</td>
<td>Ebola virus protein</td>
</tr>
<tr>
<td>VSV-EBOV</td>
<td>Ebola vaccine based on recombinant vesicular stomatitis virus</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</tbody>
</table>
References


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.


