ISSUE BRIEF

FEDERAL FUNDING IN SUPPORT OF EBOLA MEDICAL COUNTERMEASURES R&D

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PRIOR TO THE CURRENT OUTBREAK IN WEST AFRICA, Ebola garnered little global attention. Previous outbreaks elsewhere in Africa were relatively small and self-limiting, although still devastating to those communities that were affected.¹ As is the case with many other neglected tropical diseases, Ebola was not a major target for pharmaceutical research and development (R&D)—there simply was not a sufficient market demand for drugs and vaccines to cure and prevent Ebola virus infections. Yet, despite the lack of financial incentive, in 2015 we do have a number of vaccine and drug candidates in development, which may help in containing the current or future outbreaks.

The Ebola medical countermeasures (MCM)—drugs, vaccines, and diagnostics—being discussed and tested today have been developed with the significant investment in biodefense programs over the past decade. Ebola virus is a Category A priority pathogen, and it is judged to be one of a few biological agents that pose the “highest risk to national security and public health.”² Because Ebola has been identified as a Category A pathogen, the federal government has dedicated resources to developing medical countermeasures to be used in the event that Ebola is used against the US in a bioterrorism attack.

Table 1. NIAID Support for Ebola Research FY2004-13 (in \$Millions)

<i>Fiscal Year</i>	<i>Basic</i>	<i>Vaccine</i>	<i>Therapeutics</i>	<i>Diagnostic</i>	<i>Total</i>
2004	6.06	15.15	1.88		17.03
2005	8.48	16.04	4.94		20.97
2006	7.83	31.70	19.48		51.18
2007	6.43	31.18	3.09		34.27
2008	7.93	11.61	30.59	0.15	42.34
2009	15.48	20.84	6.22	0.12	27.18
2010	11.69	37.16	8.85	0.91	46.93
2011	13.80	17.57	8.67	2.84	29.08
2012	13.56	22.51	9.52	2.92	34.95
2013	131.37	17.19	10.31	1.86	29.35
Total	222.63	220.94	103.55	8.79	333.29

Note. Adapted from personal communication with NIAID. Funding amounts were provided by NIAID in September 2014. Amounts here exclude funding as part of the American Recovery and Reinvestment Act (ARRA).

Table 2. Major Experimental Ebola Medical Countermeasures in Advanced Development as of December 18, 2014

Product Name	Developer(s)	Mechanism of Action	Evidence of Efficacy	Development Phase	References
Vaccines	ChAD3	Uses chimp adenovirus 3 with glycoproteins (GP) from Ebola Sudan and Ebola Zaire	In nonhuman primates (NHP), there is 100% protection when given pre-exposure.	In Phase 1 clinical trials in the US, UK, Denmark, and Mali. Results from the US trial show an acceptable safety profile and evidence that the vaccine produced an immune response. Phase 2/3 clinical trials are beginning in early 2015 in West Africa.	6, 7, 8
	VSV-ZEBOV	Uses vesicular stomatitis virus (VSV) with Ebola Zaire GP exchanged for native VSV GP	In nonhuman primates, there has been 100% protection when given 21 days before exposure. Efficacy when given within 1 hour postexposure is 30-50%.	In Phase 1 clinical trials in Switzerland, the US, Canada, Germany, Gabon, and soon in Kenya. The Phase 1 trial in Geneva was halted due to reports of joint pain in some of the participants but has now resumed. Phase 2/3 trials are planned for early 2015 depending on the Phase 1 outcomes. This vaccine has been used in response to a laboratory accident in Germany and in some patients evacuated to the US in the current outbreak.	8, 9, 10
	VesiculoVax™ Zaire-Ebola	Recombinant VSV (N4CT1) vectored Zaire-Ebola vaccine. This platform is also used for an rVSVN4CT1-vectored Marburg vaccine and a trivalent Ebola/Marburg vaccine.	In nonhuman primates, there is 100% protection when given a single dose pre-exposure.	Phase 1 clinical trials are being planned and funded for early 2015 for both the Zaire-Ebola virus vaccine and the trivalent Ebola/Marburg vaccine.	11, 12
	MVA-BN® Ebola and Filo	Modified Vaccinia Ankara virus platform for an Ebola-Zaire vaccine and a multivalent vaccine to protect against Ebola (Zaire and Sudan) and Marburg	Preclinical testing in animals shows complete protection from Ebola Zaire species with the Ebola vaccine.	Phase 1 clinical trials have begun in the UK for the multivalent Ebola Zaire, Ebola Sudan, Marburg vaccine. Results are expected in early 2015.	13, 14
	Combination MVA-BN®/AdVac®	Recombinant, multivalent adenovirus/MVA vaccine for Ebola and Marburg	The combination vaccine has shown complete protection in preclinical testing against Ebola.	Phase 1 clinical trials began for this vaccine in January.	8, 15, 16
	EBOV GP Vaccine	Adjuvanted Ebola GP recombinant nanoparticle vaccine based on the 2014 Guinea Ebola strain	Rodent and NHP studies have shown high titers of neutralizing antibodies specific to the 2014 Guinea Ebola strain.	Phase 1 clinical trials are ongoing in Australia.	16, 17, 18
	VXA ZBOV-GP	Recombinant VSV-VECTOR vaccine used in HIV-1 vaccine candidates. Using replication-competent live oral monovalent virus vaccine (Zaire Ebola strain).	NHP studies showed complete protection with a single dose.	Phase 1 clinical study is planned for 2015 in the US.	16, 18
	Recombinant rabies vector Ebola vaccine	Inactivated recombinant rabies vaccine expresses Ebola GP	Vaccine has been shown to be safe and to induce both rabies and Ebola specific protection in non-human primates. NHP challenge studies showed complete protection against Ebola with a single dose.	Phase 1 clinical study is planned for mid-2015 in the US.	8, 18, 19

(continued)

Table 2. (Continued)

	<i>Product Name</i>	<i>Developer(s)</i>	<i>Mechanism of Action</i>	<i>Evidence of Efficacy</i>	<i>Development Phase</i>	<i>References</i>
Therapeutics with Antiviral Activity	Zmapp	Mapp (Leaf) Biopharmaceutical, DARPA, NIAID, DTRA	Triple monoclonal antibody cocktail neutralizes virus and kills infected cells.	In NHP, there is 100% treatment efficacy when initiated at 5 days postinfection.	The drug has been used under emergency investigational new drug application (eIND) for cases of compassionate use in this outbreak in Ebola-infected patients in Africa and patients evacuated to the US and Europe with inconclusive benefits. Phase 1/2 trials planned in the US and West Africa in early 2015. Few doses of the drug are available due to the current method of production in tobacco plants, which takes time. Mapp is exploring an alternative manufacturing system to increase production and has partnered with BARDA.	8, 20
	TKM-Ebola	Tekmira Pharmaceuticals, USAMRIID, DTRA	Cocktail of 2 small interfering RNAs (siRNAs) in lipid nanoparticle target the viral proteins VP35 and L polymerase to silence viral genes.	In NHP, efficacy is 83% when initiated 48 hours postinfection and 67% when initiated 72 hours postinfection.	This drug has been used under eIND for cases of compassionate use in some Ebola-infected patients in the US. A Phase 1 single ascending dose (SAD) study was completed, and discussions for Phase 1 clinical trials are under way.	20, 21
	BCX4430	BioCryst Pharmaceuticals, Inc./NIAID/USAMRIID	Small molecule, viral polymerase inhibitor	In vitro mouse studies show efficacy. NHP studies showed good protection.	Phase 1 clinical trials are under way with NIH.	20, 22
	Brincidofovir (CMX001)	Chimerix	Small molecule, viral polymerase inhibitor	In vitro activity against flaviviruses seen. Cannot evaluate in NHP due to metabolism. Used in Dallas patient unsuccessfully, but given late in the course of disease.	Human clinical trials are now under way, led by MSF at an Ebola treatment facility in Liberia. Trials are not randomized, and no patients will receive placebo. Any patients diagnosed with Ebola at the ELWA 3 treatment center can opt to receive the drug.	20, 23
	Human Convalescent Serum	N/A	Passive transfer of antibodies in human serum	A single report from the 1995 Kikwit Ebola outbreak, where 8 seriously ill patients received transfusion; 7 of 8 survived, but unable to differentiate effect of supportive care vs. use of convalescent serum. Has been used in this outbreak with indeterminate results.	WHO has issued interim guidance on the use of convalescent whole blood or plasma. Discussions about clinical trials and use during the outbreak are under way.	24
	AVI-7537	Sarepta, USAMRIID	Phospho Morpholino Oligonucleotide (PMOs) blocks viral protein production.	In NHP, treatment efficacy is 60-80% when initiated 1 hour postinfection.	Under IND for human clinical trials. Phase 1 SAD completed with no safety issues. Support for clinical trials is under consideration.	25, 26
	Favipiravir (T-705)	Medivator/Toyoma/Fujifilm/DTRA	Small molecule, viral polymerase inhibitor	In vitro mouse studies show it is less active against Ebola than influenza. NHP efficacy studies under way.	Conditionally approved in Japan for novel influenza and in Phase 3 for uncomplicated influenza. There are reports of compassionate use in Ebola patients in Europe. Phase 2/3 clinical trials began in Guinea in December 2014.	8, 27
	<i>Note.</i> Adapted from a presentation by Dr. Peter Jahrling at the JHSPH Ebola Crisis Dean's Symposium on October 15, 2014. Information has been updated. ⁸					

FUNDING FOR EBOLA COUNTERMEASURES

Table 3. Ebola Countermeasures-Related Funding in the FY2015 Omnibus (in \$Millions)

<i>Department/Agency</i>	<i>Primary Purpose of Funds</i>	<i>Appropriations Amount</i>
HHS, Food and Drug Administration (FDA)	Review, regulation, and postmarket surveillance of MCMs, and administrative activities	25
Department of Defense (DoD)	\$17 million for MCM procurement and \$95 million for MCM RDT&E	112
NIH, National Institute of Allergy and Infectious Diseases (NIAID)	Ebola countermeasures R&D	238
HHS Office of the Secretary (PHSSEF) (BARDA)	To develop and purchase countermeasures, vaccines, diagnostics, and medical supplies	733
Total		1,108.00

Note. Adapted from the text of H.R. 83, the Consolidated and Further Continuing Appropriations Act, 2015.³⁰

The US government has made sustained biodefense-related investments in basic and applied R&D aimed at producing anti-Ebola MCMs for more than a decade.³ Investments made by the National Institute of Allergy and Infectious Diseases (NIAID), through Biodefense and Emerging Infectious Diseases Program funding, and by the Department of Defense (DoD) Defense Threat Reduction Agency (DTRA), through the Chemical and Biological Defense Program (CBDP), have led to the development of a majority of the countermeasures in the pipeline.³ In addition, biodefense investments in building advanced development capabilities at the Biomedical Advanced Research and Development Authority (BARDA) and in building mechanisms for emergency clinical testing and emergency regulatory approval at the Food and Drug Administration (FDA) are now proving critical to current efforts to rapidly confirm safety and efficacy and ramp up production of countermeasures.

NIAID has been a major source of Ebola research and research support as part of the US biodefense enterprise. NIAID works to understand the pathophysiological processes that make Ebola and other Category A pathogens so worrisome to public health and national security agencies; it works to develop animal models that can be used to test the efficacy of countermeasures and develops treatment strategies for viral hemorrhagic fevers and other diseases.⁴

Since fiscal year (FY) 2004, NIAID has invested over \$333 million specifically focused on Ebola, including basic research on the virus and research toward development of vaccines, therapeutics, and diagnostics (Martin Johnson, Chief, Resource Planning and Mission Integration Branch, NIAID, NIH, personal communication, September 19, 2014) (see Table 1).

DoD has also invested in medical countermeasures development for hemorrhagic fever viruses as part of their agency-wide Chemical and Biological Defense Program. According to a press release by DoD, DTRA has invested over \$300 million since FY2003 in basic and applied research programs that work to develop vaccines, drugs, and diagnostics for Ebola and other diseases, although further breakdown of this funding was not provided by DTRA.⁵ This research has been conducted with the primary purpose of protecting the war-

fighter, yet these investments are also proving to have benefits for civilian populations. Support provided by DTRA, the US Army Medical Research Institute of Infectious Diseases (USAMRIID), and the Defense Advanced Research Projects Agency (DARPA) for research on Ebola has contributed to a number of countermeasures that may be useful in the current crisis if they are ready and scaled up in time.

As a direct result of US biodefense investments since 2003, there are at least a dozen vaccines and therapeutics in the pipeline for Ebola (see Table 2). Many of these countermeasures are currently in phase 1 clinical trials, and for some phase 2 and 3 clinical trials have begun or are being planned for 2015. A number of the therapeutics under development have been provided to Ebola-infected patients in this outbreak under “compassionate use” regulations, which allow for use of promising but experimental drugs and vaccines for patients with life-threatening illnesses.²⁸ While conclusions cannot be drawn from the few patients who have received experimental treatments, it is noteworthy that drugs and vaccines were available to give in limited quantities.

CURRENT FUNDING PICTURE

Recently, NIH and DoD have continued to provide support for advancing research into many of the countermeasures included in Table 2. They have also provided support for clinical trials and have partnered with private sector pharmaceutical companies to expand production capacity of countermeasures for use in clinical trials. Some of the funding for these efforts has been derived from current MCM budgets, and other funding has been reprogrammed. In October 2014, Congress gave approval for reprogramming \$750 million in DoD war funds to support Operation United Assistance, the deployment of military assets to assist the government of Liberia. As of December 1, 2014, \$25.6 million of the \$750 million in funding had been expended by DoD for Ebola countermeasures research and development.²⁹

Going forward, on December 16, 2014, the President signed into law the Consolidated and Further Continuing Appropriations Act, 2015, which appropriates a total of

\$5.4 billion in emergency funding to support the US response to Ebola. Of that total, approximately \$1.1 billion will go to Ebola MCM research, development, procurement, and approval (see Table 3).³⁰

FUTURE INVESTMENTS NEEDED

The current Ebola crisis has shown that investments in biodefense and health security have benefits beyond enhancing our preparedness for bioterrorism and deserve increased and sustained support over the long run.

REFERENCES

1. Outbreaks chronology: Ebola virus disease. US Centers for Disease Control and Prevention website. Updated December 18, 2014. <http://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.html>. Accessed December 18, 2014.
2. Biodefense and Emerging Infectious Diseases: NIAID emerging infectious diseases/pathogens. National Institute of Allergy and Infectious Diseases website. Updated August 8, 2014. <http://www.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/Pages/CatA.aspx>. Accessed December 19, 2014.
3. Boddie C, Sell TK, Watson M. Federal funding for health security in FY2015. *Biosecure Bioterror* 2014;12(4):163-177.
4. Emerging viral pathogens section. National Institute of Allergy and Infectious Diseases website. Updated June 1, 2011. <http://www.niaid.nih.gov/labsandresources/labs/aboutlabs/emergingviralpathogens/Pages/default.aspx>. Accessed December 18, 2014.
5. Pellerin C. DTRA medical countermeasures help West African Ebola crisis. *DoD News* December 12, 2014. <http://www.defense.gov/news/newsarticle.aspx?id=123822>. Accessed December 19, 2014.
6. Pollack A. Trial of Ebola Vaccines' Effectiveness is Announced. *New York Times* January 23, 2015. http://www.nytimes.com/2015/01/23/business/international/trial-of-2-ebola-vaccines-effectiveness-is-announced.html?_r=0. Accessed January 29, 2015.
7. NIAID/GSK experimental Ebola vaccine appears safe, prompts immune response [news release]. November 28, 2014. National Institutes of Health. <http://www.nih.gov/news/health/nov2014/niaid-28.htm>. Accessed December 19, 2014.
8. Jahrling P. Overview of lead experimental medical countermeasures for Ebola and product-specific considerations. Presentation at the JHSPH Ebola Crisis Dean's Symposium; October 15, 2014; Baltimore, MD. <http://www.jhsph.edu/events/2014/ebola-forum/ebola-forum-video-archive/deans-symposium-on-ebola-crisis-context-and-response-part-4>. Accessed December 19, 2014.
9. Merck-New Link Ebola vaccine trial resumes at lower dose: Geneva hospital. *Reuters* January 5, 2015. <http://www.reuters.com/article/2015/01/05/us-health-ebola-vaccine-idUSKBN0KE0XP20150105>. Accessed January 29, 2015.
10. NIH begins early human clinical trial of VSV Ebola vaccine [news release]. October 22, 2014. National Institutes of Health. <http://www.nih.gov/news/health/oct2014/niaid-22.htm>. Accessed December 19, 2014.
11. Profectus BioSciences receives \$9.5 million Department of Defense funding to manufacture trivalent VesiculoVax™-vectored vaccine to protect against all Ebola and Marburg viruses [news release]. October 31, 2014. Profectus BioSciences, Inc. <http://www.profectusbiosciences.net/pdfs/releases/2014%201031%20Profectus%20DoD%20Tri-V%20Ebola%20Contract.pdf>. Accessed December 19, 2014.
12. Profectus BioSciences receives \$8.6 million HHS contract to accelerate Ebola vaccine into human clinical studies [news release]. October 22, 2014. Profectus BioSciences, Inc. <http://www.profectusbiosciences.net/pdfs/releases/2014%201022%20Profectus%20Ebola%20HHS%20BARDA.pdf>. Accessed December 19, 2014.
13. Bavarian Nordic announces first subject dosed with MVA-BN Filo in a Phase 1 study investigating a new prime-boost regimen of Ebola candidate vaccines [company announcement]. December 4, 2014. Bavarian Nordic. <http://id.bavarian-nordic.com/media/news.aspx?news=4314>. Accessed December 19, 2014.
14. Bavarian Nordic enters licensing and supply agreement with Janssen on MVA-BN Ebola vaccine. October 22, 2014. Bavarian Nordic. <http://id.bavarian-nordic.com/media/news.aspx?news=4241>. Accessed December 19, 2014.
15. Akst J. Ebola update: researchers gear up for efficacy trials of experimental Ebola vaccines in Africa. *Scientist* January 12, 2015. <http://www.the-scientist.com/?articles.view/articleNo/41882/title/Ebola-Update/>. Accessed January 29, 2015.
16. Barry F. Ebola: which are the leading vaccine candidates? *BioPharma* January 27, 2015. <http://www.biopharma-reporter.com/Bio-Developments/Ebola-which-are-the-leading-vaccine-candidates>. Accessed January 29, 2015.
17. Novavax announces Ebola vaccine development program at the 8th Vaccine and ISV Conference in Philadelphia [news release]. October 27, 2014. Novavax. <http://www.novavax.com/download/releases/Novavax%20Announces%20Ebola%20Vaccine%20Development%20Program%20at%20the%208th%20Vaccine%20and%20ISV%20Conference%20in%20Philadelphia.pdf>. Accessed January 29, 2015.
18. Ebola Vaccine Landscape [PowerPoint presentation]. US Department of Health and Human Services. January 8, 2015. http://www.who.int/mediacentre/events/2015/S2.4_Robinson_ebola_MCM_landscape.pdf. Accessed January 29, 2015.
19. Ebola/Marburg: rabies vaccine protects nonhuman primates against deadly Ebola virus. National Institute of Allergy and Infectious Diseases website. Updated July 15, 2013. <http://www.niaid.nih.gov/topics/ebolaMarburg/Pages/rabiesVaccineEbola.aspx>. Accessed December 19, 2014.
20. Fact Sheet: update on the Ebola response. Official Wire website. December 2, 2014. <http://www.officialwire.com/pr/fact-sheet-update-on-the-ebola-response/>. Accessed December 19, 2014.
21. About investigational TKM-Ebola therapeutic. Tekmira website. <http://www.tekmira.com/pipeline/tkm-ebola.php>. Accessed December 19, 2014.
22. BioCryst announces study results for BCX4430 in a non-human primate model of Ebola virus infection [press release]. December 23, 2014. BioCryst. <http://investor.shareholder>.

- com/biocrypt/releasedetail.cfm?ReleaseID=888802. Accessed January 29, 2015.
23. Caulderwood K. Chimerix Ebola drug Brincidofovir begins testing in Liberia. *International Business Times* January 8, 2015. <http://www.ibtimes.com/chimerix-ebola-drug-brincidofovir-begins-testing-liberia-1777636>. Accessed January 29, 2015.
24. Experimental therapies: growing interest in the use of whole blood or plasma from recovered Ebola patients (convalescent therapies) [news release]. September 26, 2014. World Health Organization website. <http://www.who.int/mediacentre/news/ebola/26-september-2014/en/>. Accessed December 19, 2014.
25. Kroll D. FDA moves on Tekmira's Ebola drug while Sarepta's sits unused. *Forbes* August 7, 2014. <http://www.forbes.com/sites/davidkroll/2014/08/07/fda-moves-on-tekmiras-ebola-drug-while-sareptas-sits-unused/>. Accessed December 19, 2014.
26. Jarvis LM, Halford B. Unraveling Ebola. *Chem Eng News* 2014;92(48):8-15. <http://cen.acs.org/articles/92/i48/Unraveling-Ebola.html>. Accessed December 19, 2014.
27. Oestereich L, Ludtke A, Wurr S, Rieger T, Muñoz-Fontela C, Günther S. Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model. *Antiviral Res* 2014;105:17-21.
28. Understanding expanded access/compassionate use. US Food and Drug Administration website. Updated October 29, 2014. <http://www.fda.gov/forpatients/other/expandedaccess/default.htm>. Accessed December 19, 2014.
29. DOD helps fight Ebola in West Africa. Operation United Assistance. US Department of Defense website. October 2014. http://www.defense.gov/home/features/2014/1014_ebola/. Accessed December 18, 2014.
30. H.R. 83, 113th Cong. (2014). <https://www.congress.gov/bill/113th-congress/house-bill/83/all-info>. Accessed December 18, 2014.