

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

The Role of the National Institute of Allergy and Infectious Diseases Research in Addressing

Ebola Virus Disease

Testimony before the

House Foreign Affairs Committee

Subcommittee on Africa, Global Health, Global Human Rights, and International Organizations

Anthony S. Fauci, M.D.

Director

National Institute of Allergy and Infectious Diseases

September 17, 2014

Mr. Chairman and Members of the Committee:

Thank you for the opportunity to discuss the National Institutes of Health (NIH) response to the global health emergency of Ebola virus disease. I direct the National Institute of Allergy and Infectious Diseases (NIAID), the lead institute of the NIH for conducting and supporting research on infectious diseases, including viral hemorrhagic fevers such as those caused by Ebola virus infection.

For over six decades, NIAID has made important contributions to advancing the understanding of infectious, immunologic, and allergic diseases, from basic research on mechanisms of disease to applied research to develop diagnostics, therapeutics, and vaccines. NIAID has a dual mandate that balances research addressing current biomedical challenges with the capacity to respond quickly to newly emerging and re-emerging infectious diseases, including bioterror threats. Critical to these efforts are NIAID's partnerships with academia, pharmaceutical companies, international organizations such as the World Health Organization, and collaborations with other Federal entities, particularly the Centers for Disease Control and Prevention, the Food and Drug Administration (FDA), the Biomedical Advanced Research and Development Authority (BARDA), and the Department of Defense (DOD).

OVERVIEW OF EBOLA VIRUS DISEASE

Viral hemorrhagic fevers are severe illnesses that can be fatal and are caused by a diverse group of viruses including Marburg virus, Lassa virus, and Ebola virus. Infection with Ebola virus typically causes fever, severe vomiting, diarrhea, rash, profound weakness, electrolyte loss, impaired kidney and liver function, and in some cases internal and external bleeding. Since the

discovery of Ebola virus in 1976, outbreaks of hemorrhagic fever caused by Ebola virus have had fatality rates ranging from 25 percent to 90 percent, depending on the species of virus and the availability of medical facilities to care for infected patients. West Africa is currently experiencing the most severe Ebola epidemic ever recorded. As of last week, the epidemic surpassed 4,400 cumulative reported cases, including nearly 2,300 documented deaths according to CDC. The ongoing Ebola epidemic in Guinea, Liberia, Sierra Leone, Nigeria, and Senegal has generated more cases and deaths than the 24 previous Ebola outbreaks combined.

The ongoing public health crisis in West Africa demands a major amplification of efforts to identify and isolate infected individuals, perform contact tracing, and provide personal protective equipment for healthcare workers involved in the treatment of infected individuals. This still remains the time-proven approach to controlling and ultimately ending the epidemic. However, there is also a critical need to develop improved diagnostics, as well as safe and effective therapeutics and vaccines for Ebola since there are no such FDA-approved interventions available at this time. In this regard, NIAID has a longstanding commitment to advancing research to combat Ebola while ensuring the safety and efficacy of potential medical countermeasures such as treatments and vaccines.

HISTORY OF NIAID EBOLA VIRUS RESEARCH: RELATIONSHIP TO BIODEFENSE RESEARCH

The ability to safely and effectively prevent and treat Ebola virus infection is a longstanding NIAID priority. Since the 2001 anthrax attacks, NIAID has vastly expanded its research portfolio in biodefense and naturally emerging and re-emerging infectious diseases. This research targets pathogens that pose high risks to public health and national security. NIAID

has designated pathogens with high mortality such as anthrax, plague, smallpox, and Ebola virus as NIAID Category A Priority Pathogens to highlight the need for medical countermeasures against these dangerous microbes.

NIAID's expanded efforts in biodefense and emerging and re-emerging infectious diseases were undertaken with specific objectives. The first is to advance basic and translational research and facilitate development of effective products to combat deadly diseases such as Ebola. The second is to employ innovative strategies, such as broad spectrum vaccines and therapeutics, to prevent and treat a variety of related infectious diseases. The third is to strengthen our partnerships with biotechnology and pharmaceutical companies to help accelerate the availability of needed products for affected and at risk individuals.

Since 2001, NIAID's biodefense research has supported the development and testing of numerous candidate products to prevent or treat viral hemorrhagic fevers, including those caused by Ebola and other related viruses. The progress we have made with candidate vaccines, therapeutics, and diagnostics for Ebola virus would not be possible had we not made this important investment.

DEVELOPMENT AND TESTING OF EBOLA MEDICAL COUNTERMEASURES

In response to the Ebola public health emergency in West Africa, NIAID is accelerating ongoing research efforts and partnering with governments and private companies throughout the world to speed the development of medical countermeasures that could help control the current epidemic and future outbreaks. NIAID research on Ebola virus focuses on basic research to

understand how Ebola virus causes illness in animals and in people as well as applied research to develop diagnostics, vaccines, and therapeutics.

Diagnostics

Accurate and accessible diagnostics for Ebola virus infection are needed for the rapid identification and treatment of patients in an outbreak because the symptoms of Ebola can be easily mistaken for other common causes of fever in affected areas, such as malaria. NIAID continues to provide resources to investigators attempting to develop Ebola diagnostics. With NIAID support, Corgenix Medical Corporation is developing diagnostics for Ebola virus using recombinant DNA technology. NIAID also is advancing development of diagnostics, including those using novel technologies, which are capable of detecting multiple viruses including Ebola. Such innovative approaches can provide information critical to the creation of point-of-care diagnostics that could be distributed and used in areas where Ebola virus outbreaks occur. Intramural scientists from NIAID's Rocky Mountain Laboratories (RML) in Hamilton, Montana, and Integrated Research Facility in Frederick, Maryland, have responded to the epidemic by providing technical diagnostic support in Liberia.

Therapeutics

Currently, supportive care, including careful attention to fluid and electrolyte replacement, is the only effective medical intervention for patients with Ebola virus disease; no drugs are available specifically to treat Ebola virus infection. Experts are now evaluating whether drugs licensed or approved for the treatment of other diseases should be reevaluated for potential treatment of patients with Ebola in the current epidemic on an emergency basis. In parallel,

NIAID is supporting the development of novel therapeutics targeting Ebola virus. These investigational candidate therapeutics could possibly be used in clinical trials in the current epidemic and hopefully will prove to be safe and effective; if so, such treatments could be more widely available for future outbreaks. It is important to note that NIAID-supported candidate therapeutics are in early development and are currently available only in limited quantities.

NIAID has provided support to and collaborated with Mapp Biopharmaceutical, Inc., to develop MB-003, a combination of three antibodies that prevents Ebola virus disease in monkeys when administered as late as 48 hours after exposure. An optimized product derived from MB-003, known as ZMapp, has shown to be substantially more effective in animal models than earlier combinations and protected monkeys from death due to Ebola virus up to five days after infection, according to Mapp Biopharmaceutical, Inc. NIAID's preclinical services are now being used to provide pivotal safety data to support the use of ZMapp for clinical trials in humans. Mapp Biopharmaceutical, Inc., has announced that ZMapp was recently administered to humans for the first time as an experimental treatment to several Ebola-infected patients, including two Americans. It is not possible at this time to determine whether ZMapp benefited these patients. NIAID is working closely with partners at DOD, BARDA, and FDA to advance development and testing of ZMapp to determine whether it is safe and effective. BARDA has recently announced plans to optimize and accelerate the manufacturing of ZMapp so that clinical safety testing can proceed as soon as possible.

NIAID also has funded BioCryst Pharmaceuticals to develop and test BCX4430, a novel drug that interferes with the reproductive process of the virus and has activity against a broad spectrum of viruses. According to BioCryst, BCX4430 has protected animals against infection

by Ebola virus and the related Marburg virus. BioCryst has announced that a Phase 1 clinical trial of this drug is expected to begin in late 2014 or early 2015.

In related work, NIAID intramural scientists at RML are working on therapeutics that might be effective against all hemorrhagic fever viruses including the filoviruses Ebola and Marburg and the arenavirus Lassa. Ribavirin, a drug currently used to treat hemorrhagic fever viruses such as Lassa virus, is being examined for its potential use in combination therapy to treat Ebola virus infection. NIAID scientists also are studying human interferons as Ebola therapies. Other therapeutics being examined by scientists at RML are in early stages of study and if successful, will advance to animal model testing.

Vaccines

A safe and effective Ebola vaccine could be a critically important tool to help prevent Ebola virus disease and help contain future outbreaks. The hope is that such a vaccine could be licensed and used in the field to protect frontline healthcare workers and individuals living in areas where Ebola virus exists. Two Ebola vaccine candidates are entering Phase 1 clinical testing this fall. NIAID will play a critical role in advancing these Ebola vaccine candidates. The results of these Phase 1 studies will inform essential discussions about whether and how such vaccines could be of use in the current epidemic or future Ebola outbreaks.

The NIAID Vaccine Research Center (VRC) has a robust viral hemorrhagic fever vaccine development program. Since 2003, the VRC has evaluated three early-generation Ebola vaccine candidates and one Marburg vaccine candidate in Phase 1 clinical trials at the NIH campus. An additional Phase 1 clinical trial was conducted in Kampala, Uganda, in collaboration with DOD. None of the early-generation candidates raised safety concerns in these small trials; however,

they did not elicit the level of immune response thought to be needed to provide protection against exposure to the virus. The data from those trials have contributed directly to the VRC's current Ebola vaccine collaboration with the pharmaceutical company GlaxoSmithKline (GSK). VRC and GSK have developed an experimental vaccine that uses a chimpanzee virus (similar to the common cold virus), Chimp Adenovirus 3 (CA3), as a carrier, or vector, to introduce Ebola virus genes into the body; these genes code for Ebola proteins that stimulate an immune response. The vaccine candidate has shown promising results in animal models against two Ebola virus species, including the Zaire Ebola species responsible for the current epidemic in West Africa. A small Phase 1 study to examine the safety and ability of this candidate to induce an immune response in humans began on September 2, 2014, at the NIH Clinical Center in Bethesda, Maryland. Results from the study are anticipated by the end of this calendar year, and will help inform future development of the vaccine.

Additional Phase 1 clinical trials of Ebola vaccine candidates are expected to launch before the end of 2014. In October, testing will begin in the United States on a vaccine candidate derived from the CA3-vector designed to protect against a single Ebola virus species, the Zaire Ebola virus. NIAID and GSK also will donate doses of this vaccine candidate to enable testing by NIAID partners in the United Kingdom and the West African country of Mali, where existing NIAID research infrastructure will support the vaccine trial. Also this fall, NIH is collaborating with DOD and NewLink Genetics Corporation on Phase 1 safety studies of an investigational Ebola vaccine based on vesicular stomatitis virus (VSV). The VSV vaccine will serve as a vector or carrier for an Ebola gene similar to how the Chimp adenovirus served as a vector or carrier as described above for the NIAID/GSK vaccine. This vaccine candidate was developed by and licensed from the Public Health Agency of Canada.

In addition to these Ebola candidates entering Phase 1 trials in 2014, NIAID supports a broad portfolio of Ebola vaccine research, including partnering with biopharmaceutical companies. NIAID also makes preclinical services such as animal testing to advance product development available to researchers in academia and industry. More than 30 different filovirus vaccine formulations have been evaluated through NIAID's preclinical services since 2011 using animal models and assays that NIAID has developed over many years.

NIAID has supported the biopharmaceutical company Crucell to develop a recombinant adenovirus-vectored Ebola vaccine. In animal studies, this vaccine candidate protected against filovirus infection, including Ebola virus. NIAID has played an instrumental role in the recent announcements by Johnson & Johnson (parent company of Crucell) and Bavarian Nordic that they will collaborate on a two dose (prime-boost) vaccination regimen that will begin Phase 1 testing in 2015.

NIAID intramural scientists are collaborating with Thomas Jefferson University investigators to produce a vaccine candidate based on an existing rabies vaccine. The researchers aim to generate immunity to Ebola, Marburg, and rabies viruses, important diseases in certain regions in Africa. The investigators plan to pursue a version of the vaccine for human and veterinary use as well as a version for use in African wildlife. The wildlife vaccine could help prevent transmission of Ebola virus from animals to humans. The vaccine candidate for use in humans is undergoing preclinical testing and has demonstrated protection against infection by rabies and Ebola viruses in animal models. NIAID is currently partnering with DOD to produce sufficient quantities of the vaccine candidate to begin clinical testing in early 2015.

NIAID also is supporting the biotechnology company Profectus BioSciences, Inc., to investigate a second recombinant VSV-vectored vaccine candidate against Ebola and Marburg

viruses. Profectus is pursuing preclinical testing of the vaccine in preparation for a future Phase 1 clinical trial. Additionally, NIAID is collaborating with the Galveston National Laboratory & Institute for Human Infections and Immunity at the University of Texas Medical Branch at Galveston to further progress made by NIAID intramural scientists on a paramyxovirus-based vaccine against Ebola and Marburg viruses.

Other NIAID-supported efforts include Ebola virus vaccine candidates in early development, such as a DNA vaccine targeting Ebola and Marburg viruses, an adenovirus-5-based intranasal Ebola vaccine, and a combination virus-like particle/DNA vaccine targeting Ebola and Marburg viruses to be delivered by microneedle patch. Knowledge gained through these studies will further the goal of the ultimate deployment of a safe and effective vaccine that will prevent this deadly disease.

Clinical Trials

It is important to balance the urgency to deploy investigational medical countermeasures in an emergency such as the current Ebola outbreak with the need to ensure the maximal safety and to determine the efficacy of candidate drugs and vaccines for Ebola. We will do this with the strictest attention to safety considerations, established scientific principles, and ethical considerations and compassion for and realization of the immediate needs of the affected populations. The United States government, working in partnership with industry, has an established mechanism for testing and reviewing the safety and efficacy of potential medical interventions. We also have an emergent crisis in West Africa that demands a quick and compassionate response.

NIAID is committed to working with our partners to evaluate candidate drugs and vaccines for safety and efficacy. We are working to generate the evidence to show whether potential interventions are safe and effective to reassure affected communities that we are pursuing the tools needed to prevent and treat this deadly disease. Our partnerships with industry will be critical to move these products expeditiously along the development pipeline into clinical trials. NIAID is currently working to accelerate the vaccines discussed above into Phase 1 clinical trials in healthy volunteers. The data from these trials will help demonstrate whether candidate Ebola vaccines are safe in humans and are capable of generating the desired immune response. Candidate Ebola treatments will be similarly evaluated for safety and markers of potential efficacy. If successful, these candidates will be advanced to further testing in larger numbers of people. As we proceed through clinical testing, we will continue to work with our partners in the FDA to accelerate development of and speed access to the products, while also protecting the safety and rights of study volunteers.

CONCLUSION


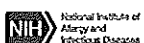
While NIAID is an active participant in the global effort to address the public health emergency occurring in West Africa, it is important to recognize that we are still in the early stages of understanding how infection with the Ebola virus can be treated and prevented. As we continue to expedite research while enforcing high safety and efficacy standards, the implementation of the public health measures already known to contain prior Ebola virus outbreaks and the implementation of treatment strategies such as fluid and electrolyte replacement are essential to preventing additional infections, treating those already infected, protecting health care providers, and ultimately bringing this epidemic to an end. We will

continue to work with biopharmaceutical companies and public health agencies throughout the world to develop and distribute medical countermeasures for Ebola virus disease as quickly as possible. NIAID remains committed to fulfilling its dual mandate to balance research on current biomedical challenges with the capability to mobilize a rapid response to newly emerging and re-emerging infectious diseases.


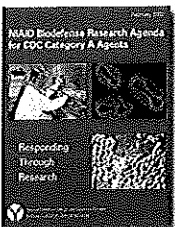
Hearing of the House Foreign Affairs Subcommittee on Africa, Global Health, Global Human Rights, and International Organizations

The Role of the National Institute of Allergy and Infectious Diseases in Research Addressing Ebola Virus Disease


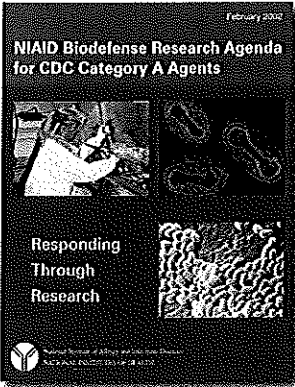
Anthony S. Fauci, M.D.
Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
September 17, 2014

9/11 Attacks

2001 Anthrax Attacks

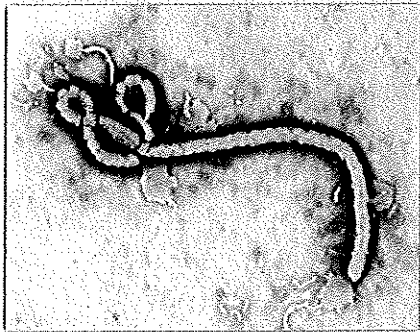
Category A pathogens

- Anthrax (*Bacillus anthracis*)
- Botulism (*Clostridium botulinum* toxin)
- Plague (*Yersinia pestis*)
- Smallpox
- Tularemia (*Francisella tularensis*)
- Viral hemorrhagic fever viruses (e.g., Ebola, Marburg, Lassa and Machupo)

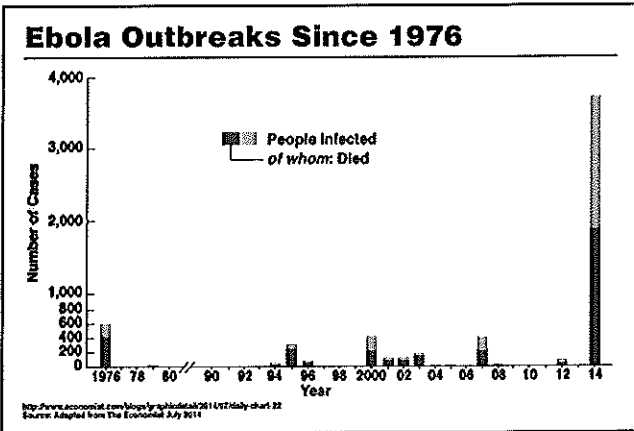
Viral Hemorrhagic Fever Viruses

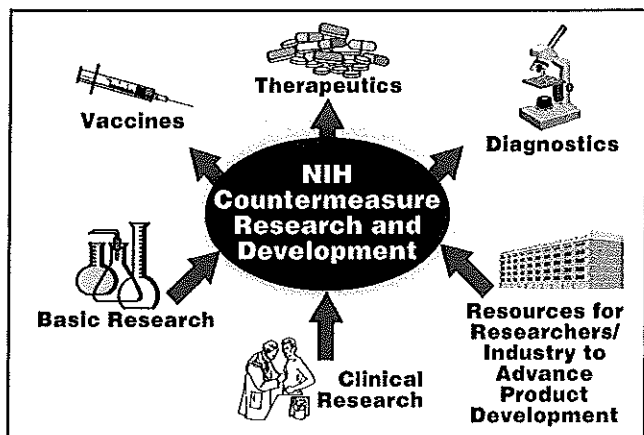
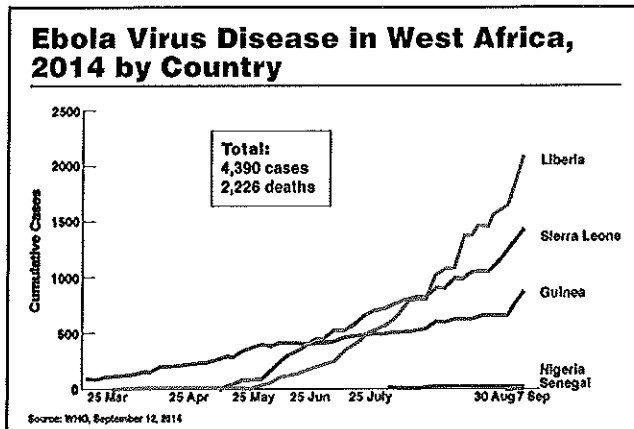
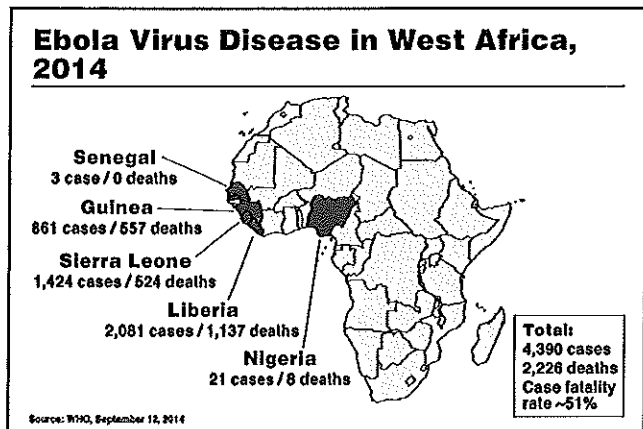
- High degree of lethality and high infectivity
- Therapy: Mainly supportive
- Vaccine: Not available at present

Ebola Virus



Source: CDC





- ### NIAID Ebola Therapeutics in Development
- **ZMapp (Mapp Biopharmaceutical)**
 - Combination of 3 artificially produced antibodies directed against the Ebola virus
 - **BCX4430 (BioCryst)**
 - A novel drug (nucleoside analogue) that interferes with the reproductive process of the virus
 - **TKM-Ebola (Tekmira Pharmaceuticals)**
 - Small inhibitory RNA molecule that interferes with the replication of the virus (supported by the Department of Defense)

ZMapp Administered to Several Individuals

DAILY NEWS August 31, 2014

Did Experimental Therapy Drug ZMapp Cure Two Americans with Ebola? Experts Can't Say, Yet

M Engel

Newsweek August 27, 2014

UK Ebola Victim Treated with Experimental Drug Zmapp

THE WALL STREET JOURNAL August 13, 2014


Ebola Virus: Infected Priest Has Died in Spain

M Moffett

GUARDIAN August 21, 2014


Liberia: Two Ebola Patients Given All Clear after ZMapp Treatment

- ### NIAID Ebola Vaccines in or Approaching Phase I Trials
- **NIAID/GSK (chimp adenovirus vector)** *Phase I trials initiated September 2014 at the NIH*
 - **NewLink (VSV vector)** *Phase I trials expected fall 2014*
 - **Crucell (adenovirus vector)** *Phase I trials expected fall 2015*
- Other vaccines in development: **Profectus (VSV vector); Bavarian Nordic (MVA vector); NIAID Intramural, Thomas Jefferson Univ. (rabies vector)**

 U.S. Department of Health and Human Services
NIH News
National Institutes of Health

National Institute of Allergy and Infectious Diseases (NIAID)
September 2014

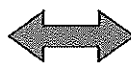
NIAID/GSK Ebola Vaccine Trial



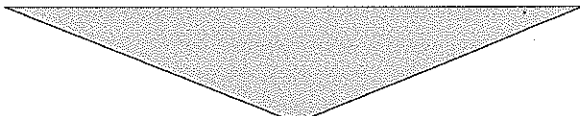
- 20 volunteers to receive vaccine to determine safety
- First volunteer received vaccine on Sept. 2
- Thus far, 10 of the 20 volunteers in the study have received vaccine

NIAID Research: A Dual Mandate

Maintain and "grow" a robust basic and applied research portfolio in microbiology, infectious diseases, immunology and immune-mediated diseases



Respond rapidly to emerging and re-emerging disease threats



New/Improved Interventions