

Ebola: The Biopharmaceutical Industry Remains Committed to Developing Medical Advances

October 2015 Update

What is Ebola?

Ebola virus disease is a severe, often fatal illness in humans. This devastating viral illness is transmitted to people from wild animals and spreads in the human population through human-to-human transmission. At onset, the disease causes flu-like symptoms, making Ebola virus disease hard to distinguish from other infectious diseases. These symptoms often worsen quickly and are then followed by diarrhea, vomiting, rash, impaired kidney and liver function, and, in some cases, internal and external bleeding.

The most recent outbreak, originating in West Africa in 2014, was the largest to date, with over 28,000 cases (suspected, probable, and confirmed) and more than 11,000 deaths.ⁱ The average fatality rate is approximately 50%, though rates in some of the West African countries affected by the recent 2014 outbreak were significantly higher.ⁱⁱ

Although there are currently no approved vaccines or treatments for Ebola, several potential candidates are in various stages of development. To date, the primary approach to treating those with Ebola has been to focus on addressing symptoms through supportive care and bolstering the patient's immune system so that he or she can fight off the infection. Biopharmaceutical companies are working together in close collaboration with government health agencies and research centers to help contain the current epidemic and accelerate advances in prevention and treatment.

Potential New Vaccines and Treatments in Development

Researchers around the world, from both the public and private sectors, are increasingly working collaboratively to develop new ways to prevent the spread of Ebola and treat patients who have contracted the virus. The research and development process for new medicines is a lengthy, challenging and complex process, which is more often than not fraught with scientific setbacks. On average it takes 10-15 years and \$2.6 billion to develop a new medicine.ⁱⁱⁱ Biopharmaceutical researchers are working to compress that timeline for Ebola projects in their pipelines.

Currently, 17 potential vaccines and treatments are in clinical trials and at least 42 more are moving through preclinical or earlier studies around the world.^{iv} Since 2000, at least 20 potential candidates have either been discontinued or suspended in development. Although these setbacks are disappointing, they have provided invaluable insights for researchers to build upon as they pursue new research tracks. A brief description of some of the potential new vaccines and treatments in development follows.

Experts at a World Health Organization (WHO) research and development summit recently discussed progress made in getting two vaccines into advanced trials and delivering commercial diagnostics to the outbreak region, the result of unprecedented global collaboration.^v Both the WHO and the U.S. Food and Drug Administration (FDA) are assessing how the results of the various research and development (R&D) efforts may be leveraged to

expedite data and results sharing and consider approaches to facilitate accelerated review and approval of promising treatments and vaccines.

In addition to developing vaccines, preventing the spread of the disease through consistent implementation of public health measures has proven effective in reducing the number of new infections of Ebola and will remain critically important.^{vi}

Overview of Selected Clinical Trials and Research Programs

Around the world, several Ebola vaccine and medicine candidates are in preclinical and early-phase clinical testing. Below is an overview of some of the clinical studies and research endeavors under way.^{vii}

Ebola ça suffit: Guinea

In April 2015, the WHO and several other international health organizations launched a Phase III trial in Guinea to assess the efficacy of the VSV-ZEBOV vaccine originally developed by the Public Health Agency of Canada, now being developed by **Merck/ NewLink Genetics Corp.**^{viii} Results from an interim analysis of the trial data were published in July 2015 and suggest that the vaccine may be safe as well as efficacious at preventing Ebola virus disease when administered via an open-label ring vaccination strategy.^{ix} In a ring clinical study, clusters of individuals who were contacts and contacts of contacts with an index case of Ebola were administered the vaccine as part of a targeted health measure; this methodology was successfully used in the smallpox eradication program.^x Interim analysis from the Ebola ring study showed 100% efficacy in the individuals the vaccine was administered to, leading the Data and Safety Monitoring Board to recommend continuation of the study.^{xi} In July 2015, study leaders announced that randomization would be discontinued to allow for all people at risk to receive the vaccine immediately, and to minimize the time necessary to gather more conclusive evidence needed for eventual licensure of the product. In addition to the ring vaccination study, Medecins Sans Frontieres (MSF) and the WHO are also studying the VSV-ZEBOV vaccine in a separate Phase II safety and immunogenicity in Guinea in front line workers.^{xii}

“Merck has an enduring commitment to develop vaccines and medicines that address the world’s most devastating infectious diseases.”

- Roger M. Perlmutter, MD, PhD, president of Merck Research Laboratories^{xiii}

PREVAIL Trial: Liberia

In February 2015, a Phase II/III trial began in Liberia to test the safety and efficacy of two vaccine candidates.^{xiv} The PREVAIL trial (Partnership for Research on Ebola Vaccines in Liberia) is being conducted through a unique partnership between the governments of Liberia and the United States National Institutes of Health (NIH) and is enrolling healthy volunteers including those who are at risk of contracting Ebola (health care and sanitation workers, for example).^{xv}

In this trial, participants are randomized to three equal-sized groups to receive a placebo (saline) injection, ChAd3-EBO-Z (a vaccine candidate that is being co-developed by the U.S. NIH’s National Institute of Allergy and Infectious Diseases [NIAID] and **GlaxoSmithKline [GSK]**), or VSV-ZEBOV (**Merck/NewLink Genetics**).^{xvi} In late March 2015, initial results from the first stage of the PREVAIL trial indicated that both vaccines appeared to be safe.^{xvii} The next stage of the trial, Phase III efficacy, has been put on hold given the reduced numbers of Ebola virus disease patients in recent months.^{xviii} Immunogenicity data from the 1,500 subjects who have been enrolled in the Phase II portion of the study should become available later in 2015.

ChAd3-EBO-Z Development Consortium

In addition to the PREVAIL trial, there are several ongoing studies of the ChAd3-EBO-Z vaccine candidate. The GSK Ebola virus candidate vaccine began clinical development in September 2014.^{xxix} The NIAID has continued to conduct non-clinical and clinical studies with other development work, including Phase I and Phase II clinical trials, supported by the Wellcome Trust, the UK Government, the Bill & Melinda Gates Foundation, the European Commission, the Swiss Government, and the U.S. Biomedical Advanced Research and Development Authority; a total of 13 clinical trials in 10 countries.^{xx}

“Understanding the urgency to launch our Ebola vaccine trials, GSK condensed development timelines from a decade to a matter of months. The Ebola crisis was a global wake-up call and underscores the need for more sustainable strategies to support multiple approaches to control Ebola as well as other biosecurity threats.”

- Moncef Slaoui, Chairman of Vaccines, GlaxoSmithKline^{xxi}

STRIVE Trial: Sierra Leone

Merck/ NewLink Genetics' vaccine candidate (VSV-ZEBOV) is also undergoing study in a third large-scale, late stage trial. A Phase II/III study to assess safety and efficacy, called the Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE), was initiated in Sierra Leone in April 2015.^{xxii} This unblinded study, being conducted in coordination with the U.S. Centers for Disease Control (CDC), uses a unique trial design with two randomized study groups: participants in one group receive the vaccine upon enrolling in the study whereas participants in the other group receive the vaccine 18-24 months later (no one receives a placebo).^{xxiii}

Phase 1, 2, and EBOVAC-Salone Trials

A prime-boost vaccine regimenⁱ is in development at the **Janssen Pharmaceutical Companies of Johnson & Johnson**. Phase I clinical studies of the vaccine regimen began in the United Kingdom and United States in January 2015^{xxiv}, followed by several sites in Africa. A Phase II study, to be carried out in the U.K. and France, started in July 2015,^{xxv} and plans are well advanced for the commencement of a large safety and immunogenicity study in Sierra Leone.^{xxvi} Preliminary data from the UK Phase I Study, presented in May to a US FDA Advisory Committee, indicate that the prime-boost vaccine regimen is immunogenic, regardless of the order of vaccine administration, and only provoked temporary reactions normally expected from vaccination.^{xxvii}

The regimen uses a prime-boost combination of two components based on AdVac[®] technology (Ad26.ZEBOV) from Crucell Holland B.V., one of the Janssen Pharmaceutical Companies, and MVA-BN[®] technology (MVA-BN-Filo) from Bavarian Nordic.^{xxviii} The vaccine regimen was discovered in a collaborative research program with the NIH. Janssen, in partnership with Bavarian Nordic, has produced drug supply for more than 800,000 regimens and is set-up to be able to produce a total of 2 million regimens of the Ebola vaccine regimen during the course of 2015.

“As a leader in the field of global health, we have a responsibility to act swiftly as Ebola continues to cause suffering among patients, families and health care workers in West Africa.”

- Alex Gorsky, Chairman and CEO of Johnson & Johnson.^{xxix}

ⁱ The prime-boost vaccine regimen in development at the Janssen Pharmaceutical Companies was funded in part with Federal funds from the National Institutes of Health, Department of Health and Human Services, under Contract Nos. HHSN272200500015C and HHSN272200900056C.

Innovative Medicines Initiative: Ebola+ Program

In January 2015, the Innovative Medicines Initiative (IMI) awarded a consortia of leading global research institutions and non-government organizations working in conjunction with the Janssen Pharmaceutical Companies grants totaling more than €100 million from the Ebola+ programme to support the development, manufacturing and deployment of the vaccine regimen.^{xxx} Organizations joining Janssen in the consortia to accelerate the development of its Ebola vaccine regimen include the London School of Hygiene & Tropical Medicine, University of Oxford, Institut National de la Santé et de la Recherche Médicale (Inserm), Inserm Transfert, Le Centre Muraz, Bavarian Nordic, Vibalogics, Grameen Foundation and World Vision of Ireland.

"It is great to see the multiple partners come together to accelerate the development of an effective vaccine both for the current epidemic and future outbreaks. This is an opportunity to make sure that this is the last Ebola epidemic in which our only tools to control it are isolation and quarantine."

- Professor Peter Piot, M.D., director of the London School of Hygiene & Tropical Medicine^{xxxii}

Phase I Inovio Trial

In May 2015, **Inovio Pharmaceuticals** initiated early-stage clinical testing of its DNA-based Ebola monoclonal antibody (dMAB) treatment.^{xxxii} Preclinical studies demonstrated 100% protection of immunized animals against experimental Ebola infection. The trial is the first step in an Inovio-headed consortium (including MedImmune, GeneOne Life Sciences, and several academic collaborators) that was selected by the U.S. Defense Advanced Research Projects Agency (DARPA) to pursue a multifaceted approach to products to prevent and treat Ebola infection, according to a company press release.

ZMapp Clinical Trial

An experimental treatment for Ebola called ZMapp began Phase I clinical testing in February through a partnership between **Mapp Pharmaceuticals**, NIAID, and the Liberian government.^{xxxiii} Zmapp is a mixture of monoclonal antibodies that was provided to several Ebola patients in August, before supplies of the medicine were exhausted. Studies in non-human primates demonstrated that the medicine had strong antiviral activity and rescued animals from death as late as five days after infection with the virus.

Amgen is working closely with Mapp Pharmaceutical and several supporting organizations, including the Bill and Melinda Gates Foundation, to explore alternative production methods for ZMapp. The investigational medicine is currently manufactured using tobacco plants and is difficult to produce in the amounts necessary for clinical testing. Researchers hope that using a more traditional method of biotechnology manufacturing will allow for more rapid scale-up of production.

"The gravity of the impact of the Ebola outbreak and Amgen's expertise in developing monoclonal antibodies provide a unique opportunity to assist in the efforts to manage this growing health-care concern."

- Kirsten Davis, Amgen^{xxxiv}

Complexity of Research and Development

Given the complexity of the disease and the unusual nature of the illnesses' origin and transmission, the development of vaccines and treatments for the Ebola virus and other similar pathogens can be very difficult. Some of the many factors contributing to the R&D challenges include the following:

- Because Ebola is not endemic to most areas around the globe, and occurs in seemingly sporadic, unpredictable outbursts, it is nearly impossible to identify an at-risk patient population to enroll in clinical trials.^{xxxv,xxxvi}
- The West African countries that are currently highly affected by this outbreak (e.g., Guinea, Liberia, and Sierra Leone) have fragmented infrastructures and health systems are basic (without even running water in many places), making them ill-equipped to give basic medical care, let alone operate clinical trials.^{xxxvii}
- Outside of an epidemic setting, the demonstration of a medicine's efficacy is restricted to animal models given that sufficient numbers of infected individuals do not exist. However, in light of the unprecedented severity of the current outbreak, the WHO has stated that it can be considered ethical to treat Ebola patients with experimental medicines.^{xxxviii}
- Because the trials tend to be fairly small, experimental medicines are often produced in relatively small quantities. In a crisis situation, manufacturing capacity must increase rapidly, but it can be difficult to do so given the complexity of the process and the unpredictability of the demand.

Humanitarian Aid to Support Those Impacted by Ebola

In addition to collaborating with the global infectious disease community to accelerate the development and manufacturing of innovative vaccines and treatments for Ebola, the biopharmaceutical industry is supporting humanitarian efforts to contain and treat the disease. These efforts include:

- Awarding grants to key humanitarian organizations to support activities in the areas directly affected by the epidemic
- Providing medicines free of charge to help treat Ebola patients with secondary infections
- Supporting education and prevention efforts through in kind and financial donations in order to prevent the spread of the virus
- Working with partners across the ecosystem to identify novel drug targets and compounds, as well as innovative study methods

In addition, the **Healthcare Ready** program, a partnership among all the stakeholders in biopharmaceutical distribution that works to maintain supplies of medicines to patients during disaster, is on standby to provide educational materials and marshal resources in the event of an outbreak in the U.S. Learn more here:

<http://www.healthcareready.org/>.

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