The emergent threat: investigating viral haemorrhagic fevers

Dr Robert Garry is leading a unique team combating diseases that not only pose an immediate risk to human life, particularly in the developing world, but also have potential applications in bioterrorism. Here he expands on the role they played in responding to the 2014 West African Ebola epidemic.

Could you give a brief introduction to your background?

I am currently managing the Viral Hemorrhagic Fever Consortium, a group of scientists who are developing countermeasures against Lassa virus, Ebola and Marburg viruses, as well as several other biodefence pathogens.

In addition, I serve in the Tulane University, USA, administration as Assistant Dean for Graduate Studies in Biomedical Sciences, and have a long-term commitment to training young scientists.

What led you to research viral haemorrhagic fever, and Lassa fever in particular?

It was initially driven by the terrorist attacks of 2001. These attacks led to increased concerns in the US about the threat of bioterrorist attacks, which led the National Institutes of Health (NIH) to increase funding for emerging attacks, which led the National Institutes of Health (NIH) to increase funding for emerging threats in locations that have minimal infrastructure. To this end, a surveillance system for Kenema District in the Eastern Province of Sierra Leone has already been developed. This ‘hub and spoke’ system will provide advanced detection of these public health threats in locations that have minimal laboratory infrastructure.

Can you discuss the collaborative nature of the Consortium and tell us why this is so important?

The Consortium is a partnership of academic and industry scientists who are developing diagnostic tests, therapeutic agents, and vaccines for Lassa fever, Ebola, and other severe diseases. No one group has the expertise to meet all the challenges of developing countermeasures to viruses such as these.

How has the team gone about investigating this disease in West Africa?

Lassa fever causes initial symptoms such as fever or headache that are common in other diseases such as malaria. Therefore, the initial focus of our Lassa fever research in post-conflict Sierra Leone was the development of improved laboratory diagnostics that would allow us to identify the disease at an earlier stage.

What role have Consortium members played in responding to the recent West African Ebola virus disease (EVD) epidemic?

Consortium scientists led by Dr Pardis Sabeti of Harvard University and the Broad Institute analysed the viral genomes from the initial EVD patients presenting to Kenema Government Hospital in Sierra Leone. Their study demonstrated that human-to-human spread, rather than repeated introductions of the virus from the animal reservoir, drove the outbreak. In addition, they also documented the expected accumulation of mutations in the viral genome.

Sequence analyses indicated that the West African variant of the virus [Makona] diverged from Central African lineages approximately a decade ago. This was consistent with serological evidence for possible exposure to filoviruses in Sierra Leoneans dating back to 2009. These genetic studies were subsequently expanded by a number of groups, including our collaborative study with the Centers for Disease Control and Prevention (CDC).

An in-depth clinical study of Ebola virus disease of the early cases admitted to KGH was also performed. Our clinical study showed that the West African variant of Ebola virus predominately causes a gastrointestinal illness. This meant we could focus attention on this aspect for control of disease spread and potential mechanisms, rather than on the bleeding manifestations that predominated in prior outbreaks.

KGH and the VHFC also worked with the US Food and Drug Administration (FDA) and WHO to validate the ReEBOV Antigen Rapid Test (ReEBOV RDT). The ReEBOV RDT received WHO Emergency Use Authorization and Listing in late February 2015, and FDA Emergency Use Authorization a few days later.

What are your future hopes for the Consortium?

First and foremost, we hope to test and deploy effective therapeutics and vaccines.

In addition, the fight against Lassa fever and EVD will require continued investment in the development of human resources and infrastructure. To this end, a surveillance system for Kenema District in the Eastern Province of Sierra Leone has already been developed. This ‘hub and spoke’ system will ultimately utilise both Lassa and Ebola RDTs and appropriate confirmatory diagnostics to provide advanced detection of these public health threats in locations that have minimal laboratory infrastructure.

Furthermore, training opportunities for West African scientists are being expanded through support by NIH’s International Center for Infectious Disease Research program, the Human Health and Heredity Program (H3Africa), Wellcome Trust, and the African Center of Excellence for the Genomics of Infectious Diseases (ACEGID).
Lassa virus is a significant threat in parts of West Africa, where it claims thousands of lives every year. The **Viral Hemorrhagic Fever Consortium** was established to understand how this virus operates, in an effort to make this region, and the rest of the world, safer.

**THE 2014 WEST** African Ebola epidemic was a global wake-up call. Suddenly, here was an incredibly deadly disease in the developing world that threatened to spill out into an unprepared West and wreak havoc.

Fortunately, despite several confirmed cases, primarily in returning health workers, in both Europe and the US, the disease remained confined primarily to the West African nations of Liberia, Sierra Leone and Guinea. Unfortunately for the residents of those countries, thousands of deaths resulted from the disease over a two-year period, and ongoing flare-ups continue to claim lives to this day.

The sad truth is that on the whole it is difficult for researchers in developed nations to combat diseases like Ebola virus disease, despite the fact that they are the ones who are best equipped to investigate them. “In the US, it is hard to get funding for diseases that primarily affect Africans and are not viewed as a threat to Americans,” explains Dr Robert Garry, Program Manager of the Viral Hemorrhagic Fever Consortium (VHFC). “However, this is changing.”

With global pandemics and bioterrorism presenting potential threats to such nations, a shift in focus is starting to emerge.

**A CONSIDERABLE THREAT**

The Consortium, based at Tulane University in Louisiana, USA, is part of this gradual change. The organisation was set up in 2010 not to target Ebola virus, which at the time did not hold the same horrifying status it does now, but instead to investigate Lassa virus infection.

Unlike Ebola, and many other viral haemorrhagic fevers, this virus does not emerge sporadically but is constantly present in West African populations, causing up to 300,000 infections and 5,000 deaths every year. While Lassa virus may not have received the same number of column inches, it too is a major threat to the people of this region.

Lassa virus is a highly infectious arenavirus, and despite its prevalence there are key areas of uncertainty when it comes to its effects.

The pathogens are spread by rodents, which are not only ubiquitous throughout West African households, but also carry the disease asymptomatically. Inhalation, ingestion or other exposure to infectious agents in the rodent faeces is enough to pass on the disease, and secondary infection from person to person can also take place. Symptoms can range from mild, flu-like conditions to multi-organ problems and death.

Crucially, the key factor under investigation by VHFC is the lack of functional antibodies produced by human bodies during acute infection by this virus. If they can overcome this, and understand how to bring about antibody-mediated neutralisation during disease onset, they should be able to produce functional treatments and vaccines.

Lassa virus is difficult to diagnose, as it presents itself much like influenza, malaria and a number of other conditions. The first goal of the Consortium was therefore to amend this situation.

**UNDERSTANDING THE ENEMY**

In a completely collaborative effort, the various partners have developed new recombinant proteins and diagnostic products, all of which have already proved effective in clinical settings across West Africa. One group would clone the proteins, another would provide expertise in antibody production, and another would express the proteins on a large scale.

Ultimately, by 2010, they were able to implement a rapid diagnostic test capable of detecting Lassa virus in just 15 minutes.
**VIRAL HEMORRHAGIC FEVER CONSORTIUM**

**OBJECTIVE**
To promote global health and safety by creating new products to diagnose, treat and significantly reduce the incidence and mortality rate of viral hemorrhagic fevers.

**KEY COLLABORATORS**
- Tulane University, USA
- Harvard University/Broad Institute, USA
- Kenema Government Hospital, Sierra Leone
- Irrua Specialist Teaching Hospital, Nigeria
- Autoimmune Technologies, LLC, USA
- Corgenix Medical Corporation, USA
- The Scripps Research Institute, USA
- University of Texas Medical Branch, USA
- Zalgen Labs, LLC, USA

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US National Institutes of Health (NIH)

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DR ROBERT GARRY’s research focuses on a number of aspects of viral pathogenesis. He was involved in collaborative studies that lead to the determination that entry proteins of enveloped viruses form at least three distinct structural classes. He continues to maintain a broad interest in the mechanisms of enveloped virus entry. He has a longstanding interest in viral diagnostics dating back to his work with the industry scientists who developed the first generation of ELISA and western blot assays to detect serum antibodies to HIV-1. These early studies on viral diagnostics lead to his characterisation of an isolate of HIV from a patient who died of AIDS in 1984, the earliest confirmed case of AIDS in the US. He is currently managing the consortium of scientists who are developing modern diagnostics for several biodefense pathogens.

More recently, a new National Institutes of Health (NIH) grant has enabled VHFC to crank their operation up a gear. Now the focus is on treatment and prevention of infection.

And that’s not all. Other arms of the VHFC are focusing on other aspects of the disease, including viral kinetics, human and viral evolution and protein structure. These projects bring together institutions that range from teaching hospitals in Nigeria to biomedical companies in the US, providing the perfect opportunity for knowledge exchange. The goal, of course, is to produce as comprehensive an image of this deadly disease as possible, so that it can be effectively dealt with whenever and wherever it arises.

**THE BIGGER PICTURE**
Of course, the development of diagnostic, therapeutic and preventive measures against Lassa virus is of immediate use to the vulnerable populations of West African countries where the pathogen is endemic, but it has a secondary function as well. Owing to their high fatality rate, ability to spread via human-to-human contact, and potential to become airborne, hemorrhagic fevers viruses are high on the list of potential biological weapons, meaning that they are a threat to the entire world. VHFC members intend to ultimately expand their operations to include Marburg and of course the famous Ebola virus, in an effort to ensure the future safety of people everywhere.

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### The Consortium

VHFC is a collaboration between an array of US and West African institutions, each of which brings their own unique expertise to the operation. Its key members are:

- **Tulane University**
  The initial grant of over $15 million was awarded to Tulane University by the National Institute of Allergies and Infectious Diseases (NIAID) to target Lassa fever.

- **Harvard University/Broad Institute**
  The primary role of Harvard is to provide expertise in the area of evolutionary adaptation in pathogens.

- **Kenema Government Hospital**
  This hospital is a crucial component of VHFC, as it exists at the epicentre of Lassa fever incidence. Kenema, located in the east of Sierra Leone, has the highest rate of the disease in the world.

- **Irrua Specialist Teaching Hospital (ISTH)**
  Another key West African member, ISTH is located in Nigeria, and is involved with investigating the prevalence and genetic diversity of the virus in that region.

- **Autoimmune Technologies, LLC**
  This New Orleans-based biomedical company produces polyclonal and monoclonal antibodies and recombinant antigens that are used by the Consortium.

- **Corgenix Medical Corporation**
  Corgenix is a key player in the development of the immunodiagnostic assay that the Consortium developed to diagnose Lassa fever in patients quickly.

- **The Scripps Research Institute**
  This institute has a few different projects that are contributing in major ways to the development of vaccines, as well as understanding host-virus interactions and the molecular basis of how viruses infect cells.

- **University of Texas Medical Branch (UTMB)**
  The research coming out of Dr Thomas Geisbert’s laboratory explores countermeasures not just against Lassa virus, but also other hemorrhagic viruses such as Ebola.

- **Zalgen Labs, LLC**
  These labs developed first-to-field-use rapid diagnostic tests for Lassa fever, a crucial development in the on-going effort to understand and combat this disease.