

Taking Down Goliaths: New Vaccines May Spell the End for Ebola, Marburg and Lassa Virus Infections

In

June and July 2005, Drs. Heinz Feldmann and Steven Jones, two health researchers funded by the Canadian Institutes of Health Research (CIHR) in collaboration with international

colleagues, announced the development of vaccines that have shown tremendous promise in defeating the Ebola, Marburg and Lassa infections in monkeys. This could translate into effective treatment for humans – and spell relief for healthcare workers on the frontline.

It's been a long fight to get to this promising stage.

A Brief History of Ebola

The Ebola virus first appeared in 1976 in western Sudan, and in a nearby region of Zaire (now the Democratic Republic of the Congo – or DRC), after significant outbreaks in Yambuku, north of the DRC, and Nzara in southern Sudan. The virus takes its name from a river in DRC.

As part of the filoviridae family, the Ebola virus assumes a characteristic filamentous form with a uniform diameter of approximately 80 nm and displays a great variation in length. No host organism for the virus has been identified, but it is believed that bats may be the source due to their ability to carry the virus and function normally (King 2003).

Symptoms include fever, intense weakness, abdominal pain, headache, sore throat, rash, diarrhea, vomiting, impaired kidney and liver function – as well as internal and external bleeding (through any orifice).

The virus can be transmitted through contact with contaminated blood, secretions or body fluids. Traditional African funerals call for relatives to lay their kin to rest by cleaning the body of the victim. This alone can cause a severe outbreak.

The incubation period of the virus lasts 2 to 21 days and, after symptom onset, death can occur within 10 days. Laboratory tests can identify the presence of Ebola through low counts of white blood cells and platelets as well as elevated liver enzymes in patient blood samples. The blood specimens can also detect specific antigens and/or genes related to the virus (World Health Organization 2004).

The first two strains identified, Ebola-Zaire (EBO-Z) and Ebola-Sudan (EBO-S), caused 431 deaths in 1976. Since then, there have been 15 other outbreaks – the most recent in 2004 in Sudan. Two other strains have emerged – Ebola-Côte d'Ivoire and Ebola-Reston – but neither has proven to be a threat among humans.

Over 1,200 people have perished due to the Ebola virus, which, while not always fatal, claims 50–90% of its victims (World Health Organization 2004).

A Brief History of Marburg

Some have called the Marburg virus a cousin to Ebola because it is also part of the filoviridae family.

The first outbreak of the virus was identified in 1967 by scientists in Marburg and Frankfurt, Germany and in Belgrade, Yugoslavia (now Serbia) who were conducting laboratory experiments on imported infected African green monkeys. Since then, there have been five outbreaks – in Angola, South Africa, Kenya and the DRC. The most recent outbreak took place in Angola in 2004 and continued into 2005.

The source of the virus is unknown.

As with Ebola, the Marburg virus can be transmitted through contact with blood or other body fluids from an infected patient or animal. Other similar symptoms include fever, diarrhea, abdominal pain, nausea, vomiting, rash and internal bleeding. The virus is detected through blood and tissue samples of patients (Centers for Disease Control and Prevention 2005a).

The incubation period for the Marburg virus is three to nine days, and death usually occurs eight to nine days after symptom onset.

Over 400 patients have died of Marburg virus infections (World Health Organization 2005a).

A Brief History of Lassa

Lassa virus was first isolated in 1969. Named after a town in Nigeria, it is part of the arenaviridae family – spherical particles whose host animal is a rat. The breed of rat, commonly known as the *Mastomys natalensis*, carries the virus through its lifetime unaffected and passes it on to humans through droppings and/or saliva in water, on the ground or in food.

This rat tends to proliferate in West Africa, specifically Guinea, Liberia, Sierra Leone and Nigeria, where cases of Lassa viral infections have increased in the past year, with several thousand deaths in Africa every year (Centers for Disease Control and Prevention, "Lassa Fever"). The fatality rate is less than Marburg and Ebola. Pregnant women are particularly vulnerable, however, with fetal loss exceeding 80% (World Health Organization 2005b).

Human-to-human transmission of Lassa virus occurs primarily through direct contact with blood, urine, throat secretions, inhalation of infective particles or sexual contact. Symptoms include fever, nausea, vomiting, diarrhea, chest pain, encephalopathy, swelling of the face and neck, cough, seizures, hypertension and painful muscles. Side effects can include hair loss, loss of coordination and deafness.

The virus can be detected through throat, blood and urine washings as well as the presence of specific antibodies. Its incubation period is 6 to 21 days, raising concerns that the virus could arrive in other countries by infected travellers who are unaware they have the disease (World Health Organization 2005b).

Ribavirin, an anti-viral drug, has proven effective in helping patients infected by the Lassa virus, but only if administered

within the first six days of infection (World Health Organization 2005b).

Protecting Healthcare Personnel

As with other transmittable diseases, front-line healthcare workers face the greatest risks. A prime example is Dr. Matthew Lukwiya, Director at St. Mary’s Hospital in Lacor, Uganda, who was one of the first to identify the Ebola virus among patients being admitted in October 2000 – and led the fight to try and contain it. Tragically, Dr. Lakiwiva was infected by a patient and he died in December of that year (TBC).

To help safeguard healthcare personnel, the DRC Ministry of Health, the U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) developed a manual for “Infection Control for Viral Haemorrhagic Fevers in the African Health Care Setting” following an Ebola outbreak in 1995.

The manual illustrates how local hospital personnel can control a virus outbreak through isolation of infected patients into restricted areas and consistent attempts at rehydration in order to sustain patient lives. It also details procedures that staff can take to minimize their risk of infection. This includes the handling of intravenous lines, needles, blood, secretions, catheters and suction devices, as well as the importance of regular bleaching of goggles, gown, gloves and patient sheets (Centers for Disease Control and Prevention 2005b).

The Progress in Vaccines

With the help of a rehometer, which simulates blood flow, Drs. Feldmann and Jones, based at the Public Health Agency of Canada (PHAC), and a Canadian research team have been able to study Ebola, Marburg and Lassa viruses under physiological conditions.

Along with Dr. Thomas Geisbert of the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), Drs. Feldmann and Jones replaced a surface protein in an animal pathogen, called vesicular stomatitis virus (VSV), with a surface protein from the Ebola, Marburg or Lassa viruses. Unmodified VSV does not cause infections in humans but can be used as a vector for proteins from other viruses. These new VSV constructs – with Ebola, Marburg or Lassa proteins inserted – were used as vaccines. Following further research, including trials with mice and guinea pigs, the PHAC scientists collaborated with USAMRIID to prove the efficiency of these vaccines in macaque monkeys.

The result? The vaccines induced protective immunity in these monkeys and completely protected them against infection from these viruses (Jones et al. 2005).

Next Steps

With the success of these vaccines in primates, the next step is to test them on humans to see if they stimulate a similar strong immune response. Dr. Jones says this will happen in about five years.

Meanwhile, both he and Dr. Feldmann are continuing to help hospital workers contain the viruses in African regions – such as the recent Marburg outbreak in Angola.

For now, Canadians can take pride in knowing that CIHR-funded researchers have made a vaccine breakthrough that will likely have positive global implications for humans, particularly in Africa. It may topple the three Goliaths of fatal hemorrhagic fevers once and for all.

References

Centers for Disease Control and Prevention. “Lassa Fever – Fact Sheet.” Retrieved September 17, 2005. <http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/Fact_Sheets/Lassa_Fever_Fact_Sheet.pdf>.

Centers for Disease Control and Prevention. 2005a. “Marburg Hemorrhagic Fever.” Retrieved September 17, 2005. <<http://www.who.int/csr/disease/marburg/factsheet/en/print.html>>.

Centers for Disease Control and Prevention. 2005b. “Infection Control for Viral Haemorrhagic Fevers in the African Health Care Setting.” Retrieved September 17, 2005. <<http://www.cdc.gov/ncidod/dvrd/spb/mnpages/vhfmanual.htm>>.

Jones, S.M., H. Feldmann, U. Ströher, J.B. Geisbert, L. Fernando, A. Grolla, H. Klenk, N.J. Sullivan, V.E. Volchkov, E.A. Fritz, K.M. Daddario, L.E. Hensley, P.B. Jahrling and T.W. Geisbert. 2005, June 5. “Live Attenuated Recombinant Vaccine Protects Nonhuman Primates Against Ebola and Marburg Viruses.” *Nature Medicine*.

King, J.W. and A. Markanday. 2003. “Ebola Virus.” Retrieved September 17, 2005. <<http://www.emedicine.com/MED/topic626.htm>>.

World Health Organization. 2004. “Ebola Haemorrhagic Fever.” Retrieved September 17, 2005. <<http://www.who.int/mediacentre/factsheets/fs103/en/print.html>>.

World Health Organization. 2005a. “Marburg Haemorrhagic Fever – Fact Sheet.” Retrieved September 17, 2005. <http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/Fact_Sheets/Marburg_Hemorrhagic_Fever_Fact_Sheet.pdf>.

World Health Organization. 2005b. “Lassa Fever.” Retrieved September 17, 2005. <<http://www.who.int/mediacentre/factsheets/fs179/en/print.html>>.

<http://www.ugandamission.net/health/news/ebola.html>

About the Author

Dr. Bhagirath Singh has been scientific director of the CIHR’s Institute of Infection and Immunity (III) since its inception. He has also served as deputy director of The John P. Robarts Research Institute (1997-2000) and co-director of the Immunology Program (1992-1997). Dr. Singh has been co-director and principal investigator in both the MRC/CIHR Juvenile Diabetes Research Foundation group in diabetes research, and the MRC immunoregulation group.