Flare-up of Ebola infection in a case a year after initial infection highlights need for continued surveillance

July 24 2018

Ebola virus may have re-emerged in a woman a year after she survived an acute Ebola virus infection, potentially leading to the infection of her husband and two of their sons, according to an outbreak report of the last known cluster of infections from a source within Liberia (occurring in November 2015), published in *The Lancet Infectious Diseases* journal.

Ebola virus can persist in immunologically protected sites of the body after recovery from acute infection, and Ebola virus RNA has previously been detected in semen, breastmilk and cerebrospinal fluid of survivors. Previously there have only been two cases of the virus re-emerging, and this new cluster is the first indication of transmission from a persistently infected female survivor of Ebola virus disease.

"Despite no current active Ebola virus transmission chains in west Africa, Ebola virus persistence could pose a continued risk for resurgence of cases and may have the potential for a large-scale outbreak, if not detected rapidly and controlled," says lead author Emily Kainne Dokubo, M.D., MPH, U.S. Centers for Disease Control and Prevention. "Further studies are needed to better understand viral persistence and transmission, and to reduce stigma against survivors. Additionally, countries and global health partners should continue to focus on strengthening health systems to prevent, rapidly detect, and respond to Ebola virus infections in the region."

Between 2014-2015, the Ebola virus disease outbreak in west Africa resulted in more than 28000 cases and 11000 deaths across Liberia, Guinea and Sierra Leone. The first case in Liberia was reported in March 2014, and infection then spread rapidly across the country, killing more than 4800 people. In May 2015, Liberia was declared free of human-to-human Ebola virus transmission.

In June 2015, a month after Liberia had been declared Ebola-free, a flare-up of a cluster of cases highlighted the potential for retransmission, but the rapid and robust response was effective in limiting additional infections, and the country was again declared free of Ebola virus transmission in September 2015.

As part of the new cluster report published today, the authors conducted an investigation of a family of six (mother, father and four sons aged 2 months, 5 years, 8 years and 15 years), and analysed the genetics of the Ebola virus detected among some of the individuals.

Health services first identified the family when the 15 year-old son showed symptoms of Ebola virus disease and tested positive in Monrovia, Liberia, on 19 November 2015. Once Ebola virus infection was confirmed, he was moved into an Ebola treatment unit but died on 23 November.

At this point, both the father and 8 year-old brother also tested positive for Ebola virus RNA, and experienced some symptoms (tiredness, headache and fever) but both recovered. The mother tested negative for Ebola virus RNA, however, she had positive Ebola virus antibodies indicating prior infection, and epidemiological investigation suggested that she survived an acute Ebola virus infection in July 2014. The authors speculate that the mother's infection re-emerged after her pregnancy, making the infection flare-up in October 2015, then transmitting the virus to her family.

Genetic analysis suggests that the virus carried by the father, the 15 year-old son and the 8 year-old son were similar, and that it was a continuation of the 2014 west African Ebola virus outbreak, when the mother suffered an acute infection after having cared for her brother who died from Ebola virus disease. The 2 month-old also had a low level of antibodies to the virus, which is likely to be caused by the transfer of maternal antibodies through breastmilk.

By assessing the family's history, the researchers ruled out travel to areas with active Ebola virus transmission, association with people who had travelled from these areas, and contact with animals that could transmit Ebola virus as the possible source of infection. Exactly how the virus was passed from family member to family member remains unclear, but the authors suggest it could be close physical contact or contact with bodily fluids.

The authors note some limitations to their study, including that the genetic analysis of the father's virus in November 2015 was incomplete. In addition, there were no available samples from the mother and the mother's brother in 2014. During this time Ebola treatment units had limited capacity to fully investigate and diagnose cases.

Writing in a linked Comment, Dr. Lorenzo Subissi, Sciensano, Belgium, highlights the large cohort of survivors of the 2013-16 Ebola epidemic in west Africa, comprising more than 17000 people, and the stigma faced by Ebola survivors: "The potential persistence of Ebola virus in body fluids was first described during the 1995 Kikwit outbreak in the Democratic Republic of Congo. Evidence has grown rapidly during and after the 2013-16 west African outbreak, when different studies reported Ebola virus persistence in survivors' immunoprivileged sites... The findings of Dokubo and colleagues' study could lead to additional stigma around survivors of Ebola because of the potential persistence of Ebola virus in their body fluids. Vaccination might become an important

strategy to control both the spread of Ebola and the stigma around it. Experts face the challenge of preparing specific communication plans adapted to the cultural context to minimise stigma around survivors of Ebola during the reintegration process in their communities. Ebola experts, under the coordination of WHO, are preparing updated recommendations on how to best structure and implement evidence-based follow-up programmes for survivors."].

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