Ebola in the United States

Robert Lindblad, MD, Ashraf El Fiky, MBBCh, PhD, and Thad Zajdowicz, MD, MPH *Rockville, Md*

The ongoing epidemic of Ebola virus in West Africa and attendant cases described in other parts of the world has focused attention on this heretofore rare disease. In this brief opinion article, we provide a short primer on the epidemiology, pathogenesis, clinical manifestations, US-based hospital preparedness, vaccine and therapy development, and control of Ebola virus disease for noninfectious disease physicians. (J Allergy Clin Immunol 2015;135:868-71.)

Key words: *Ebola, hospital preparedness, animal rule, Ebola vaccine, ZMapp*

Abbreviations used
EBOV: Ebola virus
EVD: Ebola virus disease
FDA: US Food and Drug Administration
HCW: Health care worker
RCT: Randomized controlled trial

Ebola virus (EBOV) represents one of the 2 genera that are comprised by the family Filoviridae. The EBOV genus comprises 4 species: (1) *Sudan ebolavirus*, (2) *Zaire ebolavirus*, (3) *Côte d'Ivoire ebolavirus* (also known and here referred to as *Ivory Coast ebolavirus*), and (4) *Reston ebolavirus*. EBOV (Fig 1) is an enveloped, filamentous, nonsegmented, negative-sense RNA virus with genomes of approximately 19 kb.[1] Of 7 structural genes encoded by the virus, nucleoprotein and glycoprotein are regarded as highly critical in the immunogenicity of the virus.[2,3]

EBOV outbreaks have usually occurred in sparsely populated areas of Equatorial Africa. The current EBOV epidemic in West Africa involves large urban areas to a greater extent than previous EBOV outbreaks. The natural host appears to be fruit bats, and contact with infected animals or contaminated food (fruit or bushmeat) spreads the virus to human subjects, a spillover event.[4] Transmission between human subjects then requires direct contact with body fluids from a patient who is ill with Ebola virus disease (EVD) through broken skin or contamination of mucous membranes. Contaminated objects, such as needles and syringes, can transmit EBOV as well. There is no evidence of true aerosol transmission of EBOV. The highest viral load titers occur at the time of death, and therefore appropriate safeguards are crucial during funeral preparation and disposal of the bodies of patients with EVD. This is particularly important to note because of the cultural and religious burial rituals in West African countries. After an incubation period of 3 to 21 days, EVD generally appears abruptly, with symptoms of fever, diarrhea, vomiting, and systemic inflammatory response syndrome; organ dysfunction and hemorrhagic manifestations supervene and portend death.[4]

The pathogenesis of EVD (Table I) remains poorly understood. EBOV has broad cellular tropism. Infection of hepatocellular cells and cells of the adrenal cortex can contribute to hemorrhagic tendencies, as well as fluid and electrolyte imbalances that contribute to hypotension and shock. Activation of various proinflammatory pathways, as well as production of soluble nitric acid mediators, also appear to induce apoptosis of lymphoid cells, impairing immune response to the virus. Taken together, the end results are high viral titers and multiorgan failure mimicking septic shock.[4] The ongoing EBOV epidemic in West Africa is a tragedy with complex causes: unavoidable high risk human-to-human contact in crowded urban areas, insufficient medical and public health infrastructure, local cultural aspects that increase the likelihood of spread (including local funerary practices), and inattention of developed countries for a prolonged period of time.[5]

US STATE OF PREPAREDNESS

Initial infection control protocols issued by the US Centers for Disease Control and Prevention proved insufficient. When coupled with care within US intensive care units (markedly more complex than that in West Africa), transmissions to health care workers (HCWs) occurred. The learning curve was steep, but it improved attention to personal protective equipment and procedures, and the decision in the United States to send patients with EVD to specialized biocontainment facilities (there are 4 in the United States: National Institutes of Health, Bethesda, Maryland; Emory University, Atlanta, Georgia; University of Nebraska Medical Center, Omaha, Nebraska; and St Patrick Hospital, Missoula, Montana) appears to have reduced the likelihood of spread to more HCWs in the United States. Nevertheless, all HCWs must understand that until this epidemic ends in West Africa, they have responsibility for recognizing potential patients with EVD and applying procedures to minimize the risk of exposure for themselves and others.

What are the minimum activities that HCWs in the United States must conduct at this time? First and foremost is to elicit an appropriate travel history. This is a determination not only of where patients have been but also of when they traveled and what they did while there; this information should be part of every history taken in primary and specialty care clinics. Rapid

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Corresponding author: Robert Lindblad, MD, Emmes, 401 N Washington St, Suite 700, Rockville, MD 20850. E-mail: rlindlblad@emmes.com.
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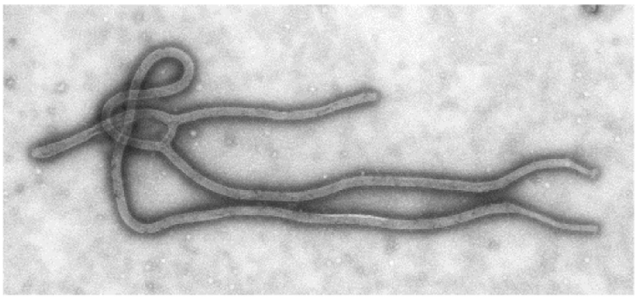

Cynthia Goldsmith/CDC

FIG 1. Electron micrograph of EBOV. EBOV and EVD were first described in 1976 in outbreaks in Sudan and northern Zaire (now Democratic Republic of the Congo).[2,3]

TABLE I. Clinical manifestations of EVD

Nonspecific, flu-like symptoms	Fever, chills, malaise, weakness, anorexia, headache, myalgias
Rash	Diffuse, erythematous, maculopapular, May desquamate
Gastrointestinal	Watery diarrhea, nausea, vomiting, abdominal pain
Hemorrhage	Petechiae, ecchymoses, mucosal hemorrhage; frank hemorrhage usually a terminal event
Other	Hiccups, chest pain, confusion, cerebral edema, seizures

screening for the presence of a fever is also critical because EBOV is not shed by asymptomatic patients, and fever is a cardinal sign of EVD. Access to and training in the use of personal protective equipment is essential for HCWs who care for patients with EVD. Training and practice are required to successfully don and doff such equipment (Fig 2). A buddy system and extensive practice should be in place in emergency departments and other facilities where patients with EVD might present, coupled with appropriate isolation rooms.[6] These measures help to ensure that inadvertent contamination does not occur (Table II).

HCWs are appropriately concerned regarding EBOV exposure; in prior epidemics in Africa, HCWs constituted a large fraction of cases, and the same is true for the current epidemic in West Africa.[6,7] The 2 cases to date contracted in the United States were both nurses in Texas caring for a man from Liberia. Nurses particularly require adequate training and support as frontline health care providers, even though hospital budgets and health care dollars are already stretched.

VACCINES AND THERAPIES FOR EBOV

Development of vaccines for pathogens such as EBOV is guided by the US Food and Drug Administration (FDA)'s Animal Efficacy Rule ("Animal Rule").[8] According to the FDA's guidance, "Approval under the Animal Rule can only be pursued if definitive human efficacy studies cannot be conducted because it would be unethical and field trials have not been feasible."[8] In this regard the FDA would permit marketing of a product after establishing evidence that it produced adequate animal efficacy results and would likely produce similar benefit in human subjects. However, use of this rule is granted only after establishing that prior safety and immunogenicity end points of the product

Athalia Christie/CDC

FIG 2. HCWs using a buddy system to don personal protective equipment before caring for a patient with EVD.

in human subjects are met, as well as demonstrating that a pathophysiologic mechanism for reduction of the virus is elucidated, information about the kinetics and pharmacodynamics of the product allows selection of an effective dose in human subjects, and a survival or disease progress prevention end point is met in an animal species that can predict results in human subjects.[8] In this case, several studies have suggested that nonhuman primates would be a reliable model for defining the "immune correlates" acting to protect against an otherwise lethal EBOV challenge. Thus far, critical immune correlates have still not been accurately identified. However, recent data point to a consistent role for IgG toward EBOV viral glycoprotein accompanied by a possible role for cellular-mediated immunity.[9,10]

There are 2 current lead examples of experimental recombinant vaccines. The first is a chimpanzee-derived replication-defective adenovirus 3–based vaccine that contains the gene encoding EBOV surface protein.[11] As of the date of this article, a phase I trial is ongoing at the National Institutes of Health's Clinical Center, Emory University, and the University of Maryland to investigate the safety, tolerability, and immunogenicity of this vaccine in healthy human volunteers.

The second candidate is a recombinant vesicular stomatitis virus–based vaccine. Trials with this vaccine are about to begin in the United States and Europe. In a recent animal study conducted in nonhuman primates, an adenoviral backbone vaccine protected all 4 experimental animals challenged with a lethal EBOV dose 5 weeks after inoculation. Furthermore, vaccine efficacy was demonstrated in 2 of the 4 animals with a booster dose.[12] Both vaccines represent collaborations between governments, pharmaceutical companies, and international health agencies. Additional vaccine candidates from other nations are proceeding for testing in healthy human volunteers, including investigation of a prime-boost strategy.

Current lead examples of promising therapies include ZMapp (Mapp Biopharmaceutical, San Diego, Calif), a drug consisting of 3 humanized mAbs capable of EBOV neutralization, and TKM-Ebola (Tekmira Pharmaceuticals, Burnaby, British Columbia, Canada), a small interfering RNA targeting 2 replication-critical EBOV genes.[13] Both are currently in very limited supply. Convalescent plasma from EVD survivors has been used as a potential therapeutic, but the results are under debate; to date, all use has