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Editorial

Lessons from Ebola and readiness for new emerging infectious threats

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Throughout history, human subjects have served as incidental hosts to many infectious diseases that have resulted in epidemics. Many of these infectious diseases are vector-borne or zoonotic in origin. In more recent times, the global spread of HIV-1, outbreaks related to avian influenza, and the emergence of severe acute respiratory syndrome and Middle Eastern respiratory syndrome, to name a few, profoundly illustrate how an infection can spread worldwide in a very rapid fashion (Table I).[1] In this issue of the *Journal*, Kampmann et al[2] and Lindblad et al[3] describe the ongoing Ebola virus disease (EVD) outbreak that is currently ravaging West Africa, and Petidemange et al[4] describe how the immune system might be promoting the viral spread and immunopathology of chikungunya virus (CHIKV) infection.

In 2013, global mortality caused by infectious disease was attributed to lower respiratory tract infections (2.7 million), HIV/AIDS (1.3 million), tuberculosis (1.3 million), and diarrheal disease (2.0 million).[5] The global burden caused by emerging and re-emerging infectious diseases is difficult to predict because the effect on human populations depends on the rate and degree to which they spread across geographic areas. Factors that can contribute to the emergence/re-emergence of infectious diseases include biological, genetic, economic, environmental, political, and social factors.[6]

EVD is a re-emerging virus in which biologic, economic, political, and social factors are all contributing to the current epidemic in West Africa. Ebola viruses, members of the Filoviridae family, were discovered in 1976 and have been responsible for major outbreaks of hemorrhagic fever in Africa since that time. From 1976-2013, the vast majority of outbreaks have occurred in remote rural locations in central African countries.[7]

The current outbreak in West Africa was first recognized in March 2014 in Guinea.[8] The outbreak quickly spread to involve neighboring Liberia and then Sierra Leone. There are intensive ongoing efforts to contain this outbreak. As of January 5, 2015, there have been in excess of 20,000 confirmed, probable, and suspected cases of EVD in Guinea, Liberia, and Sierra Leone, with more than 8000 deaths (http://www.who.int/csr/disease/ebola/situation-reports/en/?m=20150107).

The long incubation period of the disease (1-21 days) and the thousands of travelers from the affected areas that enter the United States, Europe, Asia, and other parts of Africa raised concerns for global spread of this disease. The US Centers for Disease Control and Prevention urged clinicians to be alert to the possibility of Ebola virus. Travel history to a country with ongoing EVD outbreaks should prompt isolation of subjects until symptoms and need for testing can be assessed. Use of personal protective equipment, including gowns, gloves, masks, and eye protection, along with standard infection control practices, were also recommended.[9] These recommendations proved to be insufficient when a patient from Liberia presented to a Dallas, Texas, hospital emergency department on September 25, 2014, with fever, abdominal pain, and headache and was given the misdiagnosis of sinusitis. The patient was subsequently confirmed as the first imported case of EVD. Forty-eight close contacts without the use of complete personal protective equipment were identified, including 21 health care workers with potential exposures to body fluid. All 48 contacts were placed under direct monitoring for 21 days after the last exposure. The patient died on October 8, 2014. Three days after the patient's death, a nurse involved in the patient's care had a fever and was given a diagnosis of EVD. A second nurse with similar exposure to the patient who had died presented 6 days after the patient's death with rash and fever and was also subsequently given a diagnosis of EVD.[10] Both nurses were hospitalized and recovered without incident.

The use of humanized mAbs targeting Ebola virus and convalescent plasma from EVD survivors, as well as new antivirals, are being investigated for the treatment of those with EVD.[3] Three clinical trials are expected to begin in Ebola treatment centers in Guinea and Liberia in early 2015. This has raised many issues regarding optimal clinical trial design and the ethics of not making a potentially lifesaving treatment available immediately. Although these treatment strategies provide hope, the largest challenge that remains includes addressing the cultural paradigms that have contributed to the spread of the disease and restoration of a functional health infrastructure in countries that have been plagued by war and civil unrest.[2]

Ebola virus has garnered significant media attention because of the high mortality rate and the lack of commercially available treatments. Similar media attention has not been generated for CHIKV, although the significance of this disease cannot be underestimated. CHIKV is a mosquito-transmitted RNA virus first isolated from a patient in Tanzania in 1953 during a large outbreak of severe fever associated with crippling joint aches. Since that

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TABLE I. Emerging and re-emerging infectious disease outbreaks, 2005-2014[1]

Emerging or re-emerging infectious disease	Year(s) of epidemics	Geographic distribution	No. of reported cases	No. of reported deaths
Ebola hemorrhagic virus	2014-present*	Nigeria, Sierra Leone, Mali, DRC, Liberia, Guinea, Senegal, Spain, United Kingdom, United States	20,747	8,235
	2005-2012	Uganda, DRC, RC	247	101
Chikungunya virus	2014	American Samoa	1,148	0
		Florida	11	0
	2013-2014	Caribbean Islands, including Puerto Rico and USVI	10,800 (Puerto Rico, 3,801; USVI, 183)	4
	2006	India	1.25 million	0
		Mayotte	2,833	0
		Mauritius	6,000	0
		Seychelles	8,818	0
		La Réunion Island (France)	3,115	0
Avian influenza (H7N9)	2014-present	China	11	5
Middle Eastern respiratory syndrome (MERS-CoV)	2012-present	Saudi Arabia, United Arab Emirates, Qatar, Oman, Jordan, Kuwait, Yemen, Iran, Lebanon	941	347
Lassa fever	2012	Nigeria	624	70
Pandemic H1N1 2009 influenza	2009-2010	Worldwide	651,449	18,449
Enterovirus 71	2008, 2012	Cambodia, China	4,574	76
Dengue hemorrhagic virus	2008-2012	Portugal, Cape Verde, Brazil, Madagascar, Timor-Leste	139,960	4,894
Rift Valley fever	2006-2012	Mauritania, South Africa, Madagascar, Sudan, Kenya, Somalia	1,624	379
Marburg hemorrhagic virus	2005-2014	Angola, Uganda, Netherlands	396	340
Avian influenza (H5N1)	2005-2014	Cambodia, Indonesia, Egypt, Hong Kong, Cambodia, Laos, Bangladesh, Turkey, Iraq, Azerbaijan, Pakistan, China, Thailand, Vietnam, Myanmar, Djibouti, Canada, Nigeria	649	385
Plague	2005-2014	Madagascar, Peru, China, DRC	1,423	147
Cholera	2005-2013	Mexico, Sierra Leone, DRC, RC, Haiti, Pakistan, Zimbabwe, Iraq, Guinea Bissau, Vietnam, Sudan, Angola, Benin, Burkina Faso, Guinea-Bissau, Mali, Mauritania, Niger, Senegal	334,430	11,123
Yellow fever	2005-2013	Sudan, Cameroon, DRC, Mali, Ethiopia, Chad, RC, Cameroon, Ghana, Senegal, Sierra Leone, Côte d'Ivoire, Guinea, Uganda, Central African, Republic, Liberia, Burkina Faso, Paraguay, Brazil	1,371	358

DRC, Democratic Republic of the Congo; *RC*, Republic of the Congo; *USVI*, US Virgin Islands.
*Data are current as of January 3, 2015.

time, periodic outbreaks have been reported in Asian and African countries.[11] The global spread of CHIKV has been dramatic. Within the last 10 years, the virus has spread from Africa to more than 80 countries on 5 continents, with 6 million confirmed cases and the most recent epidemics occurring in the Caribbean (Fig 1). It is noteworthy that in epidemics, cyclical transmission with a human-mosquito-human pattern can occur, allowing for rapid geographic distribution of this virus through travelers who are viremic and subsequently transmit the virus to local mosquitoes and back to human subjects.[11] This mechanism has also been seen in dengue fever, yellow fever, and West Nile virus. In addition, the more recent epidemics have been associated with a higher degree of morbidity and mortality. There is no population immunity to CHIKV in the Americas; as a result, it is anticipated that the number of cases will increase and spread to new areas in the region.[12] The role of the immune response to CHIKV suggests a correlation with degree of illness and persistence of symptoms after resolution of the initial viremia.[4]

Preventative vaccines and the use of hyperimmune globulin for treatment remain in the early stages of investigation.

What lessons have we learned from current and past epidemics caused by emerging or re-emerging diseases? First, travel and exposure history are extremely important and should be part of the standard questions asked of patients at every visit. With the increasing use of electronic medical records, development of a simplified algorithm that can question travel history at the time of intake can be used to identify patients who might be at risk.

Second, surveillance efforts are very important in identifying new or re-emerging infections. Clinicians should have a low threshold for reporting clusters of unexpected infections to their public health departments.

Third, more information about host susceptibility is needed. CHIKV was first identified as a pathogen decades ago when the prevalence of allergic disease was low. The prevalence of allergic diseases has reached epidemic proportions in the past 4 decades (more than one third of the general population). Unlike original sporadic cases when first described, the recent outbreak of CHIKV has been explosive. It is known that patients with allergic diseases, such as atopic dermatitis, are prone to disseminated viral infection, such as eczema herpeticum or eczema vaccinatum.[13] Work is needed to determine whether atopic status and the route of entry, such as intradermal inoculation of CHIKV by mosquito bites, might place patients with atopic dermatitis at high risk of disseminated viral infection. Indeed, patients with atopic dermatitis vaccinated transcutaneously have reduced neutralization antibodies to yellow fever virus that correlate with their serum IgE levels.[14] More recently, intradermal Fluzone

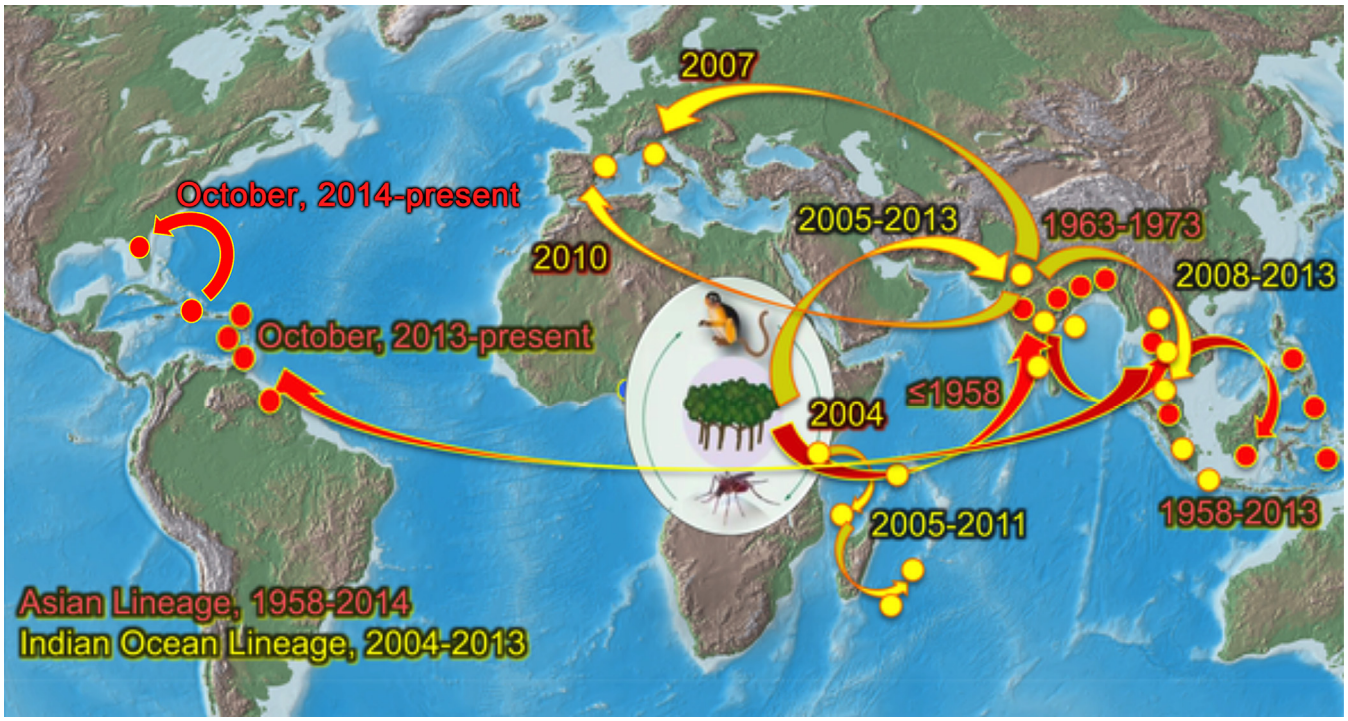

FIG 1. Spread of CHIKV from Africa to America. Figure adapted and used with permission courtesy of PLOS One - Copyright Scott Weaver. Weaver SC (2014) Arrival of Chikungunya Virus in the New World: Prospects for Spread and Impact on Public Health. PLoS Negl Trop Dis 8(6):e2921. doi:10.1371/journal.pntd.0002921.

(Sanofi Pasteur, Swiftwater, Pa) was found to induce lower influenza hemagglutination inhibition antibody titers in patients with atopic dermatitis colonized with *Staphylococcus aureus*.[15]

Lastly, research and development of vaccines and novel therapies for these types of infections are important and might be the only long-term solution to prevent further spread.

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