Ebola virus disease

Kevin B Laupland MD MSc FRCPC[1,2], Louis Valiquette MD MSc FRCPC[3]

Ebola virus disease (Ebola hemorrhagic fever) first appeared in 1976 with two concurrent outbreaks of acute viral hemorrhagic fever involving 284 cases (151 deaths [53%]) centred in Nzara, Sudan (1), and 318 cases (280 deaths [88%]) in Yambuku (near the Ebola River), Democratic Republic of Congo (2). Since these original cases, there have been approximately 20 other outbreaks occurring through to 2013, involving nearly 2500 cases in the Democratic Republic of Congo, Sudan, Gabon, Côte d'Ivoire, Uganda and the Republic of the Congo (3).

Since January 2014, a new outbreak has been identified in several West African countries (3). As of April 16, 2014, 197 cases (122 deaths [62%]) have been reported by the Ministry of Health of Guinea, of which 101 have been laboratory confirmed (56 deaths [55%]) (3). The Ministry of Health and Social Welfare of Liberia has reported 27 clinical cases with associated deaths in 13 (48%) (3). Six and 12 suspected cases occurring in the neighbouring countries of Mali and Sierra Leone have been observed, respectively, but have not been laboratory confirmed (3).

The genus *Ebolavirus* belongs to the *Filoviridae* family, along with the genus *Marburgvirus*. There are five species of Ebola virus including Bundibugyo, Zaire, Sudan, Côte d'Ivoire (Taï Forest) and Reston ebolaviruses. The former three have been responsible for the large outbreaks that have occurred in Africa, whereas the Reston ebolavirus has been observed in animals in Asia but not as a cause of human disease (4).

Fruit bats of the *Pteropodidae* family, including the species *Hypsignathus monstrosus*, *Epomops franqueti* and *Myonycteris torquata*, are believed to be the natural hosts of Ebola viruses, with humans and other mammals serving as accidental hosts (5). A range of animal accidental hosts have been documented, and Ebola virus has been implicated as one of the major causes of decline of African chimpanzee and gorilla populations in recent decades (6,7). Ebola virus is transmitted to humans through close contact with blood and bodily fluids from another infected human or animal, either by direct contact or indirectly from a contaminated environment.

The incubation period for Ebola virus disease ranges from two to 21 days and is characterized by fever, headache, myalgias and gastrointestinal symptoms (3). Multisystem involvement with hypotension and respiratory, kidney and liver failure may ensue, as well as internal and external bleeding (8). In one detailed prospective assessment of 26 of 30 hospitalized patients with Ebola virus disease during the 2007-2008 Bundibugyo outbreak, the median duration of symptoms was nine days from onset to death and 10 days from onset to discharge for survivors (9). The most common self-reported symptoms were fever (73%), nausea/vomiting (73%) and diarrhea (73%), abdominal pain (60%) and conjunctivitis (33%). The most commonly clinically documented features were severe headache (95%), asthenia (86%), myalgia (76%), dysphagia (71%), anorexia (71%) and diarrhea (67%). Among the cohort of 26 cases, seven exhibited hemorrhagic features, which included melena, prolonged bleeding at injection sites, hematemesis, bleeding gums, hemoptysis, hematuria and postpartum vaginal bleeding (9).

Definitive diagnosis of a clinically suspected case of Ebola virus disease requires laboratory confirmation. However, because of the extreme biohazard risk, testing using antigen- or antibody-based assays, or reverse transcriptase-polymerase chain reaction testing in a biosafety level 4 laboratory is required.

Case-fatality rates for the outbreaks over the past decades have varied considerably and likely reflect, at least in part, differences in diagnostic accuracy, levels of acute care provision and infecting species. Based on data from the WHO, among the 2611 cases of Ebola virus disease reported to date, 1725 deaths have occurred, resulting in an overall case-fatality rate of 66% (3). Crude case-fatality rates for the Zaire, Sudan and Bundibugyo ebolaviruses are 79%, 54% and 32%, respectively. Case-fatality rates were 71% in the 1970s, 77% in the 1990s, 61% in 2000s, and 57% during 2010 to 2013 (3). Zaire ebolavirus is responsible for the current outbreak.

Management of patients with Ebola virus disease is supportive. While there are no currently accepted specific treatments, a number of promising and novel adjuvant medical, immunotherapy and nucleic acid therapy approaches have been reported and are under further investigation (10-23).

The current outbreak is novel in that it is centred in West Africa. With the exception of a single case identified in Côte d'Ivoire in the 1990s, previous large outbreaks have been limited to countries in the central and eastern areas of the continent. If one examines the distribution of the fruit bats that are likely the natural host of the Ebola viruses, it is not surprising that cases of human disease are now being observed in Guinea and neighbouring countries (5). However, why this has occurred now remains unexplained. Furthermore, while exposure to infected bats may occur as a result of being a food source for some individuals, there are no documented cases of direct bat-to-human transmission of Ebola virus disease (24). The epidemiology of the current outbreak and its potential link with the bat population remains poorly defined and is under further active investigation (24,25).

The current outbreak highlights the importance of infection prevention and control efforts. The first reported fatal case of Ebola virus disease in the Democratic Republic of Congo in 1976 was likely iatrogenic and acquired from use of a contaminated needle for administration of parenteral chloroquine for malaria treatment of a 44-year-old man (2). In addition, as recognized in the first reported outbreaks and repeatedly thereafter, health care workers and nosocomial acquired have represented a considerable proportion of all cases. Indeed, closure of the hospital in Yambuku was reported as the most important control measure in the original 1976 outbreak in the Democratic Republic of Congo (2). In the present (2014) outbreak in Guinea, 24 health care workers have been affected, with 13 (54%) associated deaths (3). The importance of early identification and rapid laboratory confirmation of cases, as well as access to protective equipment and environmental decontamination, cannot be understated (26-30).

Ebola virus disease is rare and represents a miniscule fraction of the major infectious diseases burden in Africa. However, its high case-fatality rate, potential for human-to-human transmission and propensity to be associated with hospital-based transmission is both

[1]*Department of Medicine, Royal Inland Hospital, Kamloops, British Columbia;* [2]*Departments of Medicine, Critical Care Medicine, Pathology and Laboratory Medicine and Community Health Sciences, University of Calgary, Calgary, Alberta;* [3]*Department of Microbiology-Infectious Diseases, Université de Sherbrooke, Sherbrooke, Quebec*

Correspondence: Dr Kevin B Laupland, Royal Inland Hospital, 311 Columbia Street, Kamloops, British Columbia V2C 2T1. Telephone 250-374-5111, e-mail klaupland@gmail.com

concerning and a fertile source for hysteria (31,32). The current outbreak is defining a new geographical distribution for human Ebola virus disease. The potential for further involvement of humans and animals on a larger scale cannot be understated. With increasing globalization and ease of international travel, it appears to be inevitable that we will eventually see cases in our country (33). We can only hope that our response will be commensurate with our status as a privileged, resource-rich country.

REFERENCES

1. Ebola haemorrhagic fever in Sudan, 1976. Report of a WHO/International Study Team. Bull World Health Org 1978;56:247-70.
2. Ebola haemorrhagic fever in Zaire, 1976. Bull World Health Org 1978;56:271-93.
3. World Health Organization. Ebola virus disease, West Africa-update. Disease Outbreak News, April 17, 2014. <www.who.int/csr/don/2014_04_17_ebola/en/> (Accessed April 22, 2014).
4. Yuan J, Zhang Y, Li J, Zhang Y, Wang LF, Shi Z. Serological evidence of ebolavirus infection in bats, China. Virol J 2012;9:236.
5. Leroy EM, Kumulungui B, Pourrut X, et al. Fruit bats as reservoirs of Ebola virus. Nature 2005;438:575-6.
6. Walsh PD, Abernethy KA, Bermejo M, et al. Catastrophic ape decline in western equatorial Africa. Nature 2003;422:611-4.
7. Vogel G. Conservation biology. Can great apes be saved from Ebola? Science 2003;300:1645.
8. Paessler S, Walker DH. Pathogenesis of the viral hemorrhagic fevers. Ann Rev Pathol 2013;8:411-40.
9. Roddy P, Howard N, Van Kerkhove MD, et al. Clinical manifestations and case management of Ebola haemorrhagic fever caused by a newly identified virus strain, Bundibugyo, Uganda, 2007-2008. PloS One 2012;7:e52986.
10. Warren TK, Wells J, Panchal RG, et al. Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430. Nature 2014;508:402-5.
11. Falzarano D, Feldmann H. Possible leap ahead in filovirus therapeutics. Cell Res 2014 [Epub ahead of print].
12. Marzi A, Feldmann H. Ebola virus vaccines: An overview of current approaches. Expert Rev Vaccines 2014;13:521-31.
13. Shedlock DJ, Aviles J, Talbott KT, et al. Induction of broad cytotoxic T cells by protective DNA vaccination against Marburg and Ebola. Mol Ther 2013;21:1432-44.
14. Choi JH, Croyle MA. Emerging targets and novel approaches to Ebola virus prophylaxis and treatment. BioDrugs 2013;27:565-83.
15. Smither SJ, Eastaugh LS, Steward JA, Nelson M, Lenk RP, Lever MS. Post-exposure efficacy of oral T-705 (Favipiravir) against inhalational Ebola virus infection in a mouse model. Antiviral Res 2014;104:153-5.
16. Oestereich L, Ludtke A, Wurr S, Rieger T, Munoz-Fontela C, Gunther S. Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model. Antiviral Res 2014;105C:17-21.
17. Qiu X, Kobinger GP. Antibody therapy for Ebola: Is the tide turning around? Hum Vacc Immunother 2014;10(4) [Epub ahead of print].
18. Takada A. Do therapeutic antibodies hold the key to an effective treatment for Ebola hemorrhagic fever? Immunotherapy 2013;5:441-3.
19. Saphire EO. An update on the use of antibodies against the filoviruses. Immunotherapy 2013;5:1221-33.
20. Gehring G, Rohrmann K, Atenchong N, et al. The clinically approved drugs amiodarone, dronedarone and verapamil inhibit filovirus cell entry. J Antimicrob Chemother 2014 April 7 [Epub ahead of print]
21. Sobarzo A, Ochayon DE, Lutwama JJ, et al. Persistent immune responses after Ebola virus infection. New Engl J Med 2013;369:492-3.
22. Sobarzo A, Groseth A, Dolnik O, et al. Profile and persistence of the virus-specific neutralizing humoral immune response in human survivors of Sudan ebolavirus (Gulu). J Infect Dis 2013;208:299-309.
23. Kuehn BM. Malaria vaccine, Ebola therapy promising in early studies. JAMA 2013;310:1327-8.
24. Vogel G. Infectious disease. Are bats spreading Ebola across sub-Saharan Africa? Science 2014;344:140.
25. Polonsky JA, Wamala JF, de Clerck H, et al. Emerging filoviral disease in Uganda: Proposed explanations and research directions. Am J Trop Med Hyg 2014 February 10 [Epub ahead of print].
26. Ftika L, Maltezou HC. Viral haemorrhagic fevers in healthcare settings. J Host Infect 2013;83:185-92.
27. Shoemaker T, MacNeil A, Balinandi S, et al. Reemerging Sudan Ebola virus disease in Uganda, 2011. Emerg Infect Dis 2012;18:1480-3.
28. Callaway E. Ebola outbreak tests local surveillance. Nature 2012;488:265-6.
29. Raabea VN, Borcherta M. Infection control during filoviral hemorrhagic Fever outbreaks. J Glob Infect Dis 2012;4:69-74.
30. World Health Organization. Global Alert and Response. Interim infection control recommendations for care of patients with suspected or confirmed filovirus (Ebola, Marburg) haemorrhagic fever. <www.who.int/csr/bioriskreduction/filovirus_infection_control/en/> (Accessed May 2, 2014).
31. Gulland A. Fear spreads as number of Ebola cases in Guinea rises. BMJ 2014;348:g2644.
32. Kinsman J. "A time of fear": Local, national, and international responses to a large Ebola outbreak in Uganda. Global Health 2012;8:15.
33. Mahoney J. No confirmed cases of Ebola in Canada, health officials say. The Globe and Mail. <www.theglobeandmail.com/news/national/saskatchewan-man-tests-negative-for-ebola/article17656310/> (Accessed April 24, 2014).