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REVIEW

Ebola and Marburg virus diseases in Africa: Increased risk of outbreaks in previously unaffected areas?

Katendi Changula[1,2], Masahiro Kajihara[3], Aaron S. Mweene[1] and Ayato Takada[1,3]

[1]School of Veterinary Medicine, University of Zambia, Great East Road Campus, Lusaka, Zambia, [2]Southern African Centre for Infectious Disease Surveillance, P.O. Box, 3297, Chuo Kikuu, Morogoro, Tanzania and [3]Division of Global Epidemiology, Hokkaido University Research Center for Zoonosis Control, Sapporo 001-0020, Japan

ABSTRACT

Filoviral hemorrhagic fever (FHF) is caused by ebolaviruses and marburgviruses, which both belong to the family *Filoviridae*. Egyptian fruit bats (*Rousettus aegyptiacus*) are the most likely natural reservoir for marburgviruses and entry into caves and mines that they stay in has often been associated with outbreaks of MVD. On the other hand, the natural reservoir for ebola viruses remains elusive; however, handling of wild animal carcasses has been associated with some outbreaks of EVD. In the last two decades, there has been an increase in the incidence of FHF outbreaks in Africa, some being caused by a newly found virus and some occurring in previously unaffected areas such as Guinea, Liberia and Sierra Leone, in which the most recent EVD outbreak occurred in 2014. Indeed, the predicted geographic distribution of filoviruses and their potential reservoirs in Africa includes many countries in which FHF has not been reported. To minimize the risk of virus dissemination in previously unaffected areas, there is a need for increased investment in health infrastructure in African countries, policies to facilitate collaboration between health authorities from different countries, implementation of outbreak control measures by relevant multi-disciplinary teams and education of the populations at risk.

Key words Ebola virus, filovirus, hemorrhagic fever, Marburg virus.

Ebolaviruses and marburgviruses are single-stranded, negative-sense, non-segmented RNA viruses belonging to the family *Filoviridae*, order *Mononegavirales* (Table 1). These filoviruses are known to cause hemorrhagic fever in humans and nonhuman primates (1). Most of the known filoviruses are endemic to Africa: several different virus species belonging to the genus *Ebolavirus* have been found in central and western African rain forests, within approximately 10° north and south of the equator (2), and single species belonging to the genus *Marburgvirus* in open dry areas of eastern and south central Africa (3) (Fig. 1). The first case of MVD in Africa was reported in 1975, when a tourist who had visited Zimbabwe developed hemorrhagic fever in South Africa (4, 5). There were a few subsequent outbreaks of this disease, but after 1987 there was a period of quiescence until the DRC outbreak in 1998. The first outbreak of EVD was reported in Zaire (now the DRC) in 1976, subsequently outbreaks occurred in Sudan (now South Sudan) in 1976 and 1979 (4). These were followed by 15 years of no reported outbreaks in Africa. Since 1994, the frequency of outbreaks has increased in Africa, with discoveries of two newly found ebolaviruses in Côte d'Ivoire in 1994 (6), and in Uganda in 2007 (7); these now

Correspondence
Ayato Takada, Hokkaido University Research Center for Zoonosis Control, Kita 20 Nishi 10, Kita-ku, Sapporo 001-0020, Japan. Tel: +81 11 706 9502; fax: +81 11 706 7310; email: atakada@czc.hokudai.ac.jp

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List of Abbreviations: BDBV, Bundibugyo virus; CFR, case fatality rate; DRC, Democratic Republic of the Congo; EVD, Ebola virus disease; EBOV, Ebola virus; FHF, filoviral hemorrhagic fever; LLOV, Lloviu virus; MARV, Marburg virus; MVD, Marburg virus disease; RC, Republic of Congo; RAVV, Ravn virus; RESTV, Reston virus; SUDV, Sudan virus; TAFV, Taï Forest virus.

Table 1. Current filovirus taxonomy

Order (70)	Family	Genus	Species	Virus
Mononegavirales	*Filoviridae*	*Marburgvirus*	*Marburg marburgvirus*	Marburg virus
				Ravn virus
		Ebolavirus	*Zaire ebolavirus*	Ebola virus
			Sudan ebolavirus	Sudan virus
			Taï Forest ebolavirus	Taï Forest virus
			Bundibugyo ebolavirus	Bundibugyo virus
			Reston ebolavirus	Reston virus
		Cuevavirus	*Lloviu cuevavirus*	Lloviu virus

belong to the species *Taï Forest ebolavirus* and *Bundibugyo ebolavirus*, respectively (4).

In most previous FHF outbreaks, there were usually one or a few primary introductions of infection to humans, after which spread occurred by human to human transmission (8, 9). There were however, multiple, short, independent chains of human-to-human transmission in the 1998 MVD outbreak in the DRC, at least nine genetic lineages of the virus being involved, and multiple independent chains of transmission from infected non-human primates in the 2001 EVD outbreaks in Gabon and the RC (9, 10). Some outbreaks of EVD are thought to be associated with hunting and processing of bush meat, whereas MVD outbreaks have often been associated with entry into caves or working/decommissioned mines (9–11). Primary infection is followed by human to human transmission via contact with body fluids of infected individuals (8, 12). There is usually a delay between the initial cases and the diagnosis of FHF. This is attributable to the remoteness of most affected areas, their ill-equipped medical facilities and the fact that signs and symptoms of FHF are mainly non-specific, leading to FHF being misdiagnosed as other more frequent infections that are endemic to the area (8, 13). While it is possible that some cases have occurred without virus-specific laboratory diagnosis, outbreaks of FHF have been increasingly reported (14–16). This review paper looks at recent FHF outbreaks in Africa and discusses the potential risk of such outbreaks in previously unaffected areas.

RECENT MVD OUTBREAKS

The genus *Marburgvirus* has one species, *Marburg marburgvirus*, with two viruses, namely MARV and RAVV (17). Egyptian fruit bats (*Rousettus aegyptiacus*) were recently found to be the most likely natural reservoir host for marburgviruses (18). Many outbreaks have been associated with entry into working/decommissioned mines or caves (2, 11, 19) in which the bats stay.

The most recent MVD outbreaks occurred in Uganda in 2012 (Table 2). MARV infections in Egyptian fruit bats have been found to have seasonal fluctuations, with biannual peaks that correspond to infections in humans (18). The 2012 outbreak occurred during one of the peaks of MARV infections in bats. The full length genome sequences from this outbreak showed 99.3% sequence identity to MARV from bats captured in 2008 and 2009 in a nearby cave (20). In 2007 there were two independent outbreaks in Uganda, occurring in miners who had had close contact with bats. In June 2007, three people were infected and one died, whereas in the later outbreak there was only one case and no mortality (11).

Table 2. Chronology of Marburg virus disease outbreaks in Africa

Year	Country	Virus	Cases	Deaths	CFR (%)
1975 (12, 61)	South Africa (from Zimbabwe)	MARV	3	1	33
1980 (12, 61)	Kenya	MARV	2	1	50
1987 (12, 61)	Kenya	RAVV	1	1	100
1998–2000 (12, 61)	DRC	MARV RAVV	154	128	83
2004–2005 (12, 61)	Angola	MARV	252	227	90
2007 (11, 21)	Uganda	MARV	3	1	33
		RAVV	1	0	0
2012 (20, 61)	Uganda	MARV	15	4	27

There was 21% sequence variation between the full-length RNA genomes of these viruses, the earlier one being closely related to historical MARV sequences and the later one more closely related to RAVV, which was first isolated in Kenya in 1987. Both MARV- and RAVV-related sequences were also found in fruit bats (*R. aegyptiacus*) in the same area (21).

The 2004–2005 MVD outbreak in Angola was the first report of MVD outside East Africa. There was very little genome sequence variation between the viruses isolated during the outbreak, some being 100% identical. Despite the large geographic distance between Angola and the other known locations of MVD, phylogenetic analysis using the complete viral genome sequences put Angolan strains within the same clade as the majority of east African isolates (22). Whereas CFR for MVD are variable (Table 2), the MARV-Angola strain is thought to be more pathogenic than other MARV strains such as the Musoke strain (23–25).

RECENT EVD OUTBREAKS

There has been an increase in EVD outbreaks in Africa, probably as result of increased contact between humans and wildlife because of extensive deforestation, hunting and mining (14). Ebolavirus species have complete genome sequence divergence of 30–45% (7). The CFRs of the different ebolavirus species causing these EVD outbreaks have also varied (Table 3).

Ebola virus representing the species *Zaire ebolavirus* can cause sporadic infections in humans, usually resulting in self-limiting outbreaks (26). The genetic diversity between EBOV strains so far isolated is low (27). For instance, two separate outbreaks caused by EBOV occurred in Luebo in the DRC in 2007 and 2008: the sequences of the viruses in these two outbreaks were almost identical and related to previously isolated strains, including the one causing the first reported outbreak in Yambuku in the DRC in 1976 (28). Most recently, there was an outbreak of hemorrhagic fever caused by EBOV in the West African countries of Guinea, Liberia and Sierra Leone. Full genome sequences of EBOV from three patients showed 97% nucleotide sequence identity to DRC and Gabon strains of EBOV (29, 30). TAFV, an ebolavirus belonging to a different species (namely, *Taï Forest ebolavirus*) has been found in the Taï Forest, Côte d'Ivoire (6); however, the outbreak in West Africa was the first ever reported incidence of

Table 3. Chronology of Ebola virus disease outbreaks in Africa

Year	Country	Virus	Cases	Deaths	CFR (%)
1976 (62)	DRC	EBOV	318	280	88
1976 (62)	South Sudan	SUDV	284	151	53
1977 (62)	DRC	EBOV	1	1	100
1979 (62)	South Sudan	SUDV	34	22	65
1994 (62)	Côte d'Ivoire	TAFV	1	0	0
1994 (62)	Gabon	EBOV	52	31	60
1995 (62)	DRC	EBOV	315	250	79
1996 (62)	Gabon	EBOV	37	21	57
1996–1997 (62)	Gabon	EBOV	60	45	75
1996 (62)	South Africa	EBOV	2	1	50
2000–2001 (62)	Uganda	SUDV	425	224	53
2001–2002 (62)	Gabon	EBOV	65	53	82
2001–2002 (62)	RC§	EBOV	57	43	75
2002–2003 (62)	RC	EBOV	143	128	90
2003 (62)	RC	EBOV	35	29	83
2004 (62)	South Sudan	SUDV	17	7	41
2005 (71)	RC	EBOV	12	10	83
2007 (62)	DRC	EBOV	264	187	71
2007 (62)	Uganda	BDBV	149	37	25
2008–2009 (62)	DRC	EBOV	32	15	47
2011 (62)	Uganda	SUDV	1	1	100
2012 (62)	Uganda	SUDV	11	4	36
2012 (62)	DRC	BDBV	36	13	36
2012 (62)	Uganda	SUDV	6	3	50
2014 (72)†	Guinea	EBOV	398	264	66
2014 (72)†	Liberia	EBOV	33	24	73
2014 (72)†	Sierra Leone	EBOV	97	49	51

†Situation as of 18 June 2014. The numbers include confirmed, probable and suspected cases.

EBOV infection in this region (31). In the 2001–2004 EVD outbreaks in the RC and Gabon, nonhuman primates were also affected by EBOV infections, a large decline occurring in their populations just before and during the outbreaks in humans in the same area (10, 32). A large serological survey during the 2001–2002 outbreak in Gabon found that dogs might be asymptomatically infected with EBOV, probably as a result of eating infected carcasses or licking body fluids from infected patients, and might potentially transmit EBOV infections (33).

As opposed to EBOV, SUDV, representing the species *Sudan ebolavirus*, is much more confined geographically, all outbreaks having occurred within a 640 km range (27). Genetic diversity between the different SUDV strains is very low (27). In 2011, 7 years after its last appearance, there was a fatal case of SUDV infection in Uganda; the full-length genome sequence of the isolate showed 99.3% identity to the one that caused the Gulu outbreak in 2000 (34). There were two distinct outbreaks caused by SUDV, with independent chains of transmission, in Uganda in 2012 (20) (Table 3). In each of the outbreaks there was high sequence identity between the strains isolated within each individual outbreak. The strain causing the outbreak in November of the same year had the closest sequence identity to the Gulu 2000 outbreak strain (20).

The first recorded outbreak caused by BDBV, representing the species *Bundibugyo ebolavirus*, occurred in Uganda in 2007 (7) (Table 3). The virus was found again in a 2012 outbreak in Isiro in the DRC: this was the first identification of BDBV in the DRC. The BDBV isolate showed 98.6% full genome sequence identity with the prototype BDBV isolated in the 2007 outbreak in Bundibugyo, Uganda (20).

GEOGRAPHICAL DISTRIBUTION OF FILOVIRUSES

While FHF outbreaks have been reported in few countries in Africa (Fig. 1, Tables 2 and 3), the geographical distribution of filoviruses may be wider than previously thought. A feature of recent outbreaks is new strains/species in new locations, as has been the case with the MVD outbreak in Angola, the discovery of BDBV in Uganda and the DRC, and the current EBOV infection in West Africa (7, 20, 29, 35). Using ecological niche modeling, filovirus distribution was generally predicted to occur across the Afro-tropics, with ebolaviruses occurring in the central and western African rain forests and marburgviruses in the drier and less forested central and eastern Africa (3). Countries like Tanzania, Mozambique, Madagascar and Mauritania have had no reported outbreaks of filovirus infections, but do fall within the ecological niche of this virus and its reservoir(s). It is possible that there have been misdiagnosed and undiagnosed cases in countries with no FHF outbreak history. In some areas with no recorded outbreaks of EVD, EBOV seroprevalence in humans and some species of nonhuman primates has been found to be unexpectedly high (32, 36). This suggests either the presence of non-pathogenic variants of EBOV or unknown filoviruses antigenically similar to EBOV, but with lower pathogenicity, causing high seropositivity (32, 37–39). This also implies high exposure of these populations to the virus (36). Wider filovirus distribution, even into the Eurasian continent, has been suggested by recent studies that have reported the discovery of RESTV in domestic pigs in China (40); identification of a new filovirus, LLOV in Spain (41) and detection of antibodies to filoviruses or unknown filovirus-related viruses in Indonesian orangutans (42) and fruit bats in Bangladesh (43).

POTENTIAL ROLE OF BATS IN FILOVIRUS TRANSMISSION

Apart from *R. aegyptiacus*, the only bat species from which infectious marburgviruses have been isolated, other bat species in which filovirus genome RNAs have been detected are *Epomops franqueti, Hypsignathus monstrosus* and *Myonycteris torquata* for EBOV (44); *Miniopterus inflatus* and *Rhinolophus eloquens* for MARV (45), and *Miniopterus schreibersii* for LLOV (41). Many more bat species have been found to have antibodies to various filoviruses (46). The ranges of distribution of the above mentioned bat species in which EBOV and MARV RNAs have been detected are within many countries in which outbreaks have occurred (47). In general, it is thought that bats and many potential pathogens have co-evolved and circulated for thousands of years, with a recent increased spillover of zoonotic pathogens to humans. Human encroachment into previously uninhabited areas is a contributing factor (48, 49).

Eidolon helvum is a straw-colored migratory fruit bat, its primary habitat being in equatorial Africa. It is found in large colonies in Angola, Cote d'Ivoire, Malawi, Mauritania, Nigeria, Uganda and Zambia (50), often roosting in trees within towns as well as on islands in rivers or lakes (51). Between mid-October and late December each year, major *E. helvum* colonies, comprising 5–10 million bats in all, congregate in the Central Province of Zambia (50). Some bat colonies have been shown to migrate more than 2500 km (52). While ebolavirus has never been isolated from these bats, ebolavirus-specific antibodies have been detected in

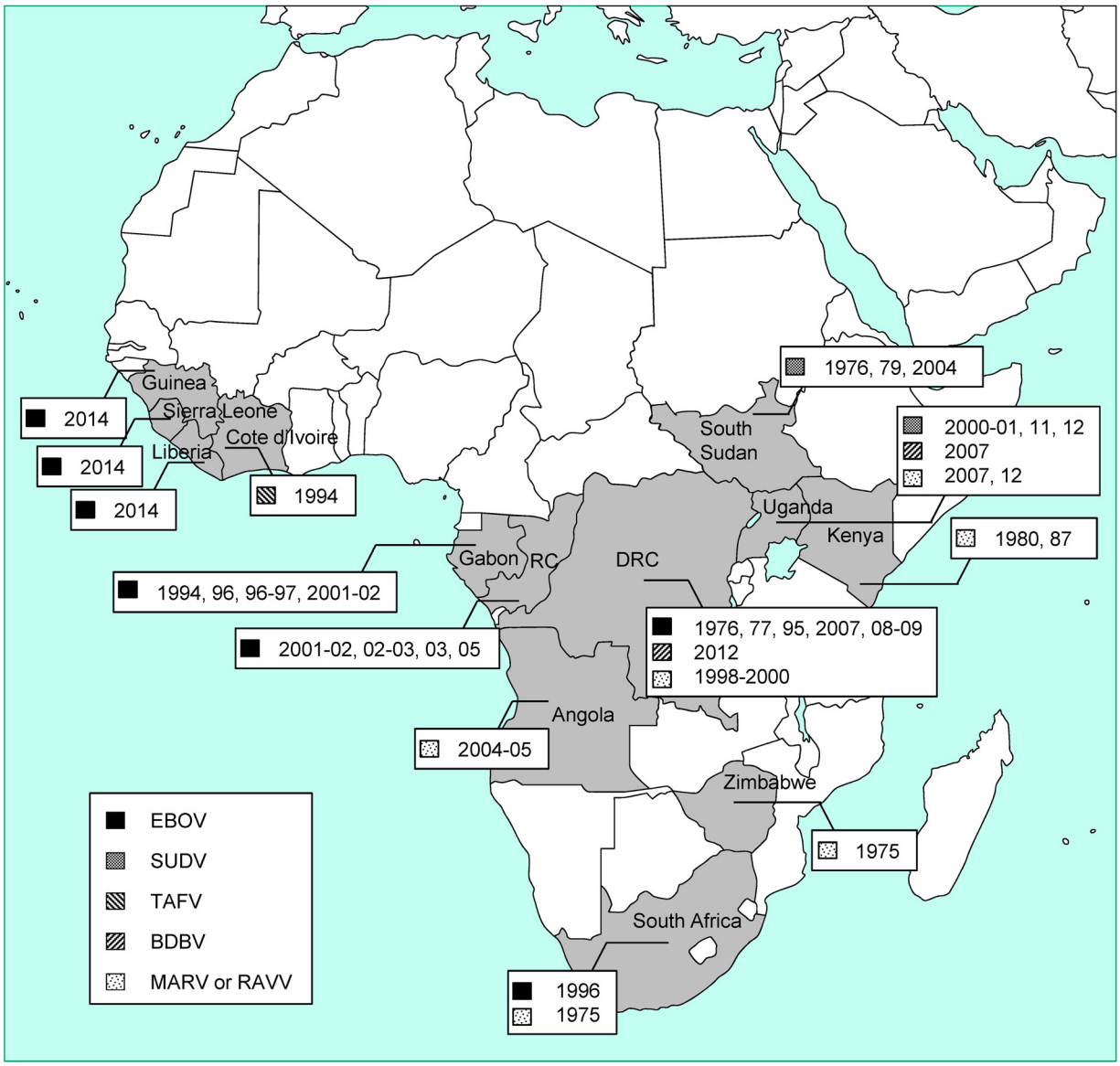

Fig. 1. Location of FHF outbreaks in Africa. Countries that have reported outbreaks are shaded in gray. Causative filovirus species and the years of outbreaks are shown in white boxes. Situation as of 18 June 2014.

blood samples from one bat (53). If these bats shed infectious virus, they could potentially transmit ebolavirus infection between their primary habitats and their migratory sites, putting a large part of sub-Saharan Africa at risk of infection.

Filovirus ecology is not yet well understood. Although bats appear to play an important role in filovirus transmission (46), other animal species, including pigs (54), dogs (33), duikers (10) and nonhuman primates, may be involved (10, 32). Although the effects of climate change on infectious diseases are poorly understood, it likely affects wildlife habitats and densities, which has the potential to increase the frequency of disease outbreaks by increasing risk of exposure of humans to reservoir hosts and/or because of increased viral loads in these reservoir hosts (55).

POSSIBLE ANTHROPOGENIC FACTORS CONTRIBUTING TO FREQUENT OUTBREAKS OF FHF IN AFRICAN COUNTRIES

An increasing population with an increasing demand for resources has forced people to intrude into previously

uninhabited land for agricultural and mining activities, potentially bringing humans into contact with unknown pathogens, reservoir hosts and/or amplifying hosts (15, 56). Wildlife trade, much of which is conducted informally and/or illegally, can also increase the risk of outbreaks. Contact between hunters, middlemen and consumers and wildlife could increase the possibility of disease transmission from infected animals (57). Associations between hunting/butchering/eating of infected carcasses and outbreaks of EVD have been reported (10, 38). The only recorded human case of TAFV was in a researcher who contracted the infection by performing autopsies on chimpanzees (58). The source of infection in the 2007 outbreak of EVD in the DRC was reportedly traced back to freshly killed bats bought for consumption (59). Index cases in the 2001 EVD outbreaks in Gabon and the RC acquired the infection from handling animal carcasses (10).

Increase in travel has also increased the risk of exposure of human populations to infected people and/or animals (15, 60). MARV was imported by tourists from Zimbabwe to South Africa in 1975 and from Uganda to the USA and the Netherlands in 2008 (61). EBOV was also imported into South Africa from Gabon by a medical practitioner in 1996 (62). In the most recent outbreak of EVD in West Africa, the disease was first reported in southern Guinea forests; this was followed by dissemination into other districts as well as the capital city, Conakry (31). The disease was also spread to Liberia from individuals who had a recent history of travel to Guinea and two patients suspected of having EVD died in Guinea and were repatriated to Sierra Leone for burial (63).

During outbreaks, several factors increase the risk of further spread of the disease. Outbreaks usually occur in regions that are resource poor and consequently have severely constrained health services, lack of personal protective equipment and medical health personnel who have knowledge of the disease, especially risk factors for infection (8, 30). Ignorance in the communities affected also plays a large role in further transmission of the disease. In the recent West African outbreak, there were reports of communities in denial, some people believing the disease was caused by the devil, or was brought in by politicians and even foreign medical personnel, the result being that infected individuals and their families did not want to seek medical attention (30, 64, 65).

Though there have been no recorded outbreaks of filovirus infection caused by displacement of people from areas of war and civil strife, there is potential for transmission of diseases to new areas in such situations (56), as in the case of the increased risk of reemergence of lymphatic filariasis in Thailand from Burmese refugees (66, 67). There are currently over 2.6 million internally displaced persons in the DRC and over 450,000 refugees in neighboring countries (68). Inter-ethnic conflict in South Sudan has resulted in a large number of internally displaced persons as well as refugees. South Sudan also hosts refugees from other countries, including the DRC (69).

CONCLUSION

As discussed above, there is great potential for new outbreaks of FHF in previously unaffected areas. Various human activities such as increased travel and trade, encroachment into forests and caves, civil strife, and war, as well as wildlife activities relating to the ecology of filoviruses, may all contribute to opportunities for the spread of filoviruses from their reservoir hosts. To counter or mitigate these potential threats, there is a need for both sentinel laboratories and regional referral laboratories to help in the monitoring and surveillance of FHF. Increased investment in health infrastructure and development of diagnostic tests that are affordable and can be used in areas with limited diagnostic capability are also required. For these to work successfully, policies to facilitate collaboration between health authorities from different countries need to be implemented. To enhance control measures in areas experiencing FHF outbreaks, leaders in both affected and at risk areas need to be educated on the disease and its risk factors in order to facilitate dissemination of appropriate information to the community.

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DISCLOSURE

The authors declare no conflict of interest.

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