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Ebola virus disease: a literature review

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ABSTRACT

Ebola virus disease (EVD) is a life-threatening viral disease with a fatality rate ranging from around 30% to 90%. The first EVD outbreak was reported in the 1970s in Zaire (now the Democratic Republic of the Congo). Until 2013, most outbreaks occurred in the Central Africa region, including Zaire, Sudan and Uganda. However, between March and October 2014, over 10 000 cases of EVD have been recorded in West Africa, such as in Guinea, Liberia, Sierra Leone, and Nigeria, and a few hospital or secondary infections of EVD have occurred in Spain and the United States of America. EVD is presently one of the world's most feared diseases. In this literature review, we describe the epidemiology, clinical features, diagnosis, and treatment of EVD.

1. Introduction

Ebola virus (EBOV) belongs to the family Filoviridae, the genus *Ebolavirus*, and frequently causes fatal infection in humans[1]. EBOV disease (EVD) may show multiple, serial, and nonspecific-disease symptoms including high fever, headache, vomiting, anorexia, diarrhea, and aching muscles[1-4]. Unexplained bleeding in the eyes, nose, gums, and gut occurs in the advanced stages[1-4]. The first outbreak of EVD was reported in 1976 in the Democratic Republic of the Congo[5]. Since then, there have been reports of small EVD outbreaks in some countries in Central Africa, including Sudan and Uganda[1,6], with an estimated 2 350 cases of EVD occurring between the1970s and 2013. The disease can therefore be regarded as endemic to some areas of Central Africa.

In March 2014, an outbreak of EVD was reported for the first time in West Africa, in Guinea, and it spread rapidly to neighboring countries including Liberia and Sierra Leone, creating a serious epidemic[7]. This has caused major health concerns both in and beyond the region, with the World Health Organization (WHO) and numerous countries initiating health monitoring and containment measures[8,9]. We describe here the previous and current epidemics, epidemiology, clinical features, diagnosis, and treatment of EVD as described to date in the literature.

2. EVD epidemics from the 1970s to 2013

Summarized epidemics data from the 1970s to 2013 are shown in

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Table 1. EVD first emerged in 1976 in the Democratic Republic of Congo (DRC) and at around the same time in Sudan. Among these epidemic areas, 318 cases were recorded in DRC [case fatality rate (CFR): 88%] and 284 cases in Sudan (CFR: 53%)[5]. As the first reports of the epidemic occurred near the Ebola River, DRC, the disease became known as Ebola hemorrhagic fever (EHF)[7,10], and two different species of EBOV were confirmed: EBOV-Zaire (EBOV-Z) and EBOV-Sudan (EBOV-S). In 1977, one fatal case due to EBOV-Z was reported in Zaire, and EBOV-S subsequently reemerged with 34 cases, 22 of which were fatal, in Sudan in 1979.

No further cases were recorded until 1994, when a new species of EBOV was confirmed in a non-fatal case in the Ivory Coast and named EBOV-IC. One case was confirmed who had traveled from Liberia to Sierra Leone and had antibodies to EBOV, suggesting existence of EBOV-IC in Liberia[11]. These episodes suggest that EBOV had spread from areas in Central Africa to West Africa. In 1995, EVD due to EBOV-Z reemerged in the DRC[12]. An estimated 315 cases and 250 deaths (CFR: 81%) occurred during this large epidemic. The EBOV-Z species identified was shown to have a close genetic relationship with the strains isolated in 1976 in Zaire[13]. EBOV-S then emerged in Uganda during 2000-2001, resulting in an estimated 425 cases and 224 deaths (CFR: 53%). The EBOV species identified could be clearly placed among the EBOV-S strains isolated in 1976 in Sudan[1,14,15]. In 2004, an EBOV-S outbreak of 17 cases and 7 deaths (CFR: 41%) was reported in Yambio County, South Sudan. The index case had butchered a monkey, and human-to-human transmission was mainly through direct contact[16]. Outbreak of EBOV-Z occurred in the Republic of Congo in 2002-2003 with 143 cases (128 deaths, CFR: 89%) and in the DRC in 2007, with 264 suspected cases and 187 deaths (CFR: 71%) recorded[17,18]. In November 2007, a new EBOV species, designated Bundibugyo ebolavirus (EBOV-B), was identified in Western Uganda, and 149 suspected cases and 37 deaths had been reported by January 2008 as the outbreak neared conclusion[19]. In the 2008 Ebola outbreak, there were 32 cases including 15 deaths (CFR: 47%) in Kasai Occidental Province in the DRC[20,21]. In May 2011, a patient with suspected EHF died after contacting EBOV-S in Luwero District, Uganda[22], and the following year an outbreak among 11 patients resulted in 4 deaths from EHF in Kibaale District[23]. Another EVD outbreak occurred in the DRC

Table 1

Outbreaks of EVD from 1970s to 2014*.

Year	Outbreak location	Species	Human cases		
			Reported number of human cases	Reported number of deaths among cases	CFR (%)
1976	Democratic Republic of the Congo (formerly Zaire)	Zaire	318	280	88
1976	Sudan (South Sudan)	Sudan	284	151	53
1976	England	Sudan	1	0	0
1977	Zaire	Zaire	1	1	100
1979	Sudan (South Sudan)	Sudan	34	22	65
1989	USA	Reston	0	0	0
1990	USA	Reston	4 (asymptomatic)	0	0
1989-1990	Philippines	Reston	3 (asymptomatic)	0	0
1992	Italy	Reston	0	0	0
1994	Gabon	Zaire	52	31	60
1994	Côte d'Ivoire (Ivory Coast)	Taï Forest	1	0	0
1995	Democratic Republic of the Congo	Zaire	315	250	81
1996 (January-April)	Gabon	Zaire	37	21	57
1996-1997 (July-January)	Gabon	Zaire	60	45	74
1996	South Africa	Zaire	2	1	50
1996	USA	Reston	0	0	0
1996	Philippines	Reston	0	0	0
1996	Russia		1	1	100
2000-2001	Uganda	Sudan	425	224	53
October 2001-March 2002	Gabon	Zaire	65	53	82
October 2001-March 2002	Republic of the Congo	Zaire	57	43	75
December 2002-April 2003	Republic of the Congo	Zaire	143	128	89
November-December 2003	Republic of the Congo	Zaire	35	29	83
2004	Sudan (South Sudan)	Sudan	17	7	41
2004	Russia	Zaire	1	1	100
2007	Democratic Republic of Congo	Zaire	264	187	71
December 2007-January 2008	Uganda	Bundibungyo	149	37	25
November 2008	Philippines	Reston	6 (asymptomatic)	0	0
December 2008-February 2009	Democratic Republic of the Congo	Zaire	32	15	47
May 2011	Uganda	Sudan	1	1	100
June-October 2012	Uganda	Sudan	11*	4	36
June-November 2012	Democratic Republic of the Congo	Bundibugyo	36*	13	36
November 2012-January 2013	Uganda	Sudan	6*	3	50
March 2014-Present	Various contries	Zaire	15 113*	5 406	36

*: These data are based on earier reports[1-28]; CFR: Case fatality rate.

in 2012, and 13 of the 36 laboratory-confirmed cases died[24,25]. None of the abovementioned outbreaks had epidemiologic links[1].

3. Initial EVD epidemiology in 2014

An epidemiologic investigation of laboratory-confirmed cases indicated that the first fatality of the current 2014 outbreak occurred in December 2013 in Guinea[4]. The patient was a 2-year-old child, and 8 other deaths were confirmed between December 2013 and February 2014 in the same village (Meliandou village, Guéckédou Prefecture). The disease may have spread from some of these patients to others in neighboring prefectures such as Macenta, Nzérékoré, and Kissidougou[4]. Guéckédou and Macenta prefectures are bordered to the north by Liberia and Sierra Leone. The epidemiologic investigation reported 15 fatal laboratory-confirmed EVD cases[4]. EBOV-Z was identified as the causative agent and phylogenetic analysis suggested that an independent cluster had formed from the previously identified EBOV strains from the DRC and Gabon[4].

4. EVD epidemics in West Africa in 2014

The relatively small EVD outbreaks in Guinea may have spread to neighboring countries such as Liberia and Sierra Leone[26]. As of 16 November 2014, 15 113 EVD cases have been reported (confirmed, probable and suspected cases) in eight countries since the epidemic began. Among them, 5406 deaths have occurred (CFR: 35.8%)[27]. As of November 2014, EVD cases in Guinea, Liberia, and Sierra Leone amount to 1971 (CFR: 60.4), 7069 (CFR: 41.9%) and 6073 (CFR: 20.6%), respectively[27], with some cases being reported further afield in Mali, Nigeria, and Senegal[27]. Four EVD patients reported in the United States of America and one in Spain have all involved in medical personnel or those who worked in the epidemic areas[27]. Detailed geometric data are shown in Figure 1.

5. Virology of EBOV

EBOV belongs to the family *Filoviridae* and the genus *Ebolavirus*[1,10]. Five EBOV species have been identified: EBOV-Z, EBOV-S, EBOV-IC, EBOV-B, and Reston ebolavirus. The prefix of the family name "filo" originates from the Latin word for thread or string. Virions have multiple morphological forms of very long filamentous rods or compact convoluted shapes (diameter around 80 nm, length 800-14000 nm)[1]. The EBOV genome is a single negative-sensed RNA (genome size 19 Kb). The virions contain 7 proteins: nucleoprotein, viral proteins 24, 30, 35, and 40, glycoprotein (GP), and L protein. The structure of the genome is similar among the species, but phylogenetic analysis has shown the species have formed independent lineages with wide genetic divergence (Figure 2). Notably, the virulence of each species may differ markedly from the others[1,3]. For example, EVD cases due to EBOV-Z and EBOV-S show high CFRs of over 70% and 50%, respectively, while the CFR for EBOV-B is around 27%[3,28]. Reston ebolavirus may have low or no virulence in humans, but it is thought that the virus is highly virulent in simians[1].

Phylogenetic analysis based on the *GP* gene sequences of EBOV detected in patients from the current epidemic areas have been confirmed as EBOV-Z strains and they have close genetic relationships

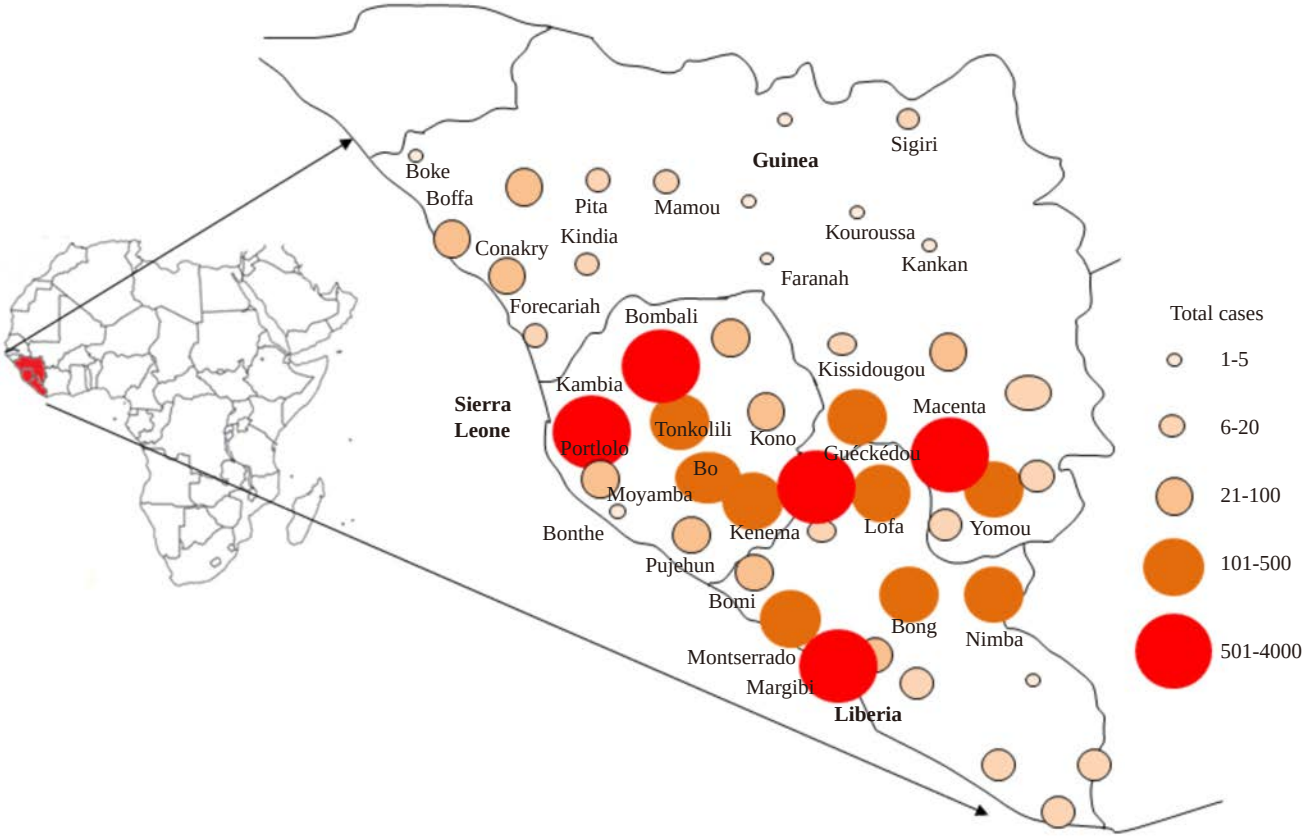

Figure 1. Detailed geometric data of the EVD outbreak.
The data shown are based on a report by the WHO[28].

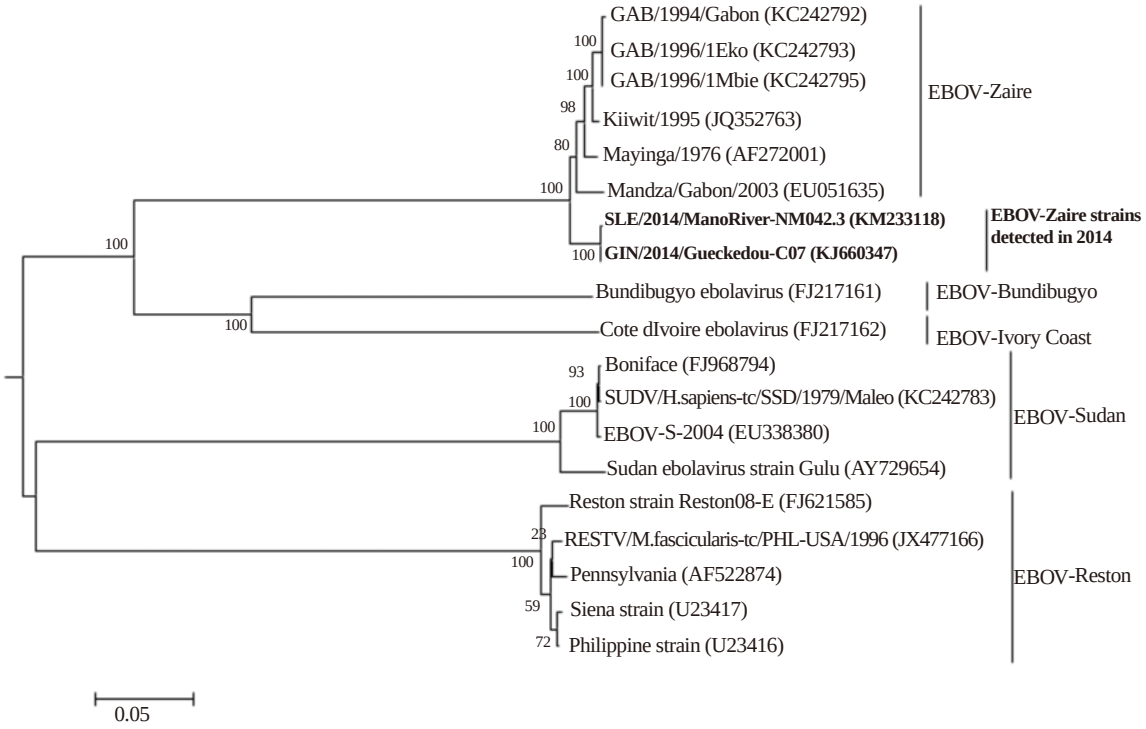

Figure 2. Phylogenetic tree of Ebola virus *GP* gene.
Distances were calculated according to Kimura's 2-parameter method and the tree was plotted by the neighbor-joining method (1 000 bootstrap replications). Numbers at each branch indicate the bootstrap values of the clades supported by that branch.

(Figure 2)[28,29]. However, the genetic properties of these strains may be different from typical EBOV-Z[29]. In addition, the CFR for the present EBOV-Z epidemics is relatively low (around 40%-50%) compared with typical EBOV-Z[30], while in a recent report with laboratory confirmed cases, the CFR is 74% in Sierra Leone[31]. The reason for the difference in virulence among the strains is not known.

6. Transmission routes

Although the life cycles of EBOV species are not precisely known, the natural hosts (reservoirs) of EBOV are thought to be a species of fruit bat[32,33]. It is known that EBOV can transmit from bats to some species of simians[9], so EBOV-infected bats and simians may be an infectious source of EBOV when handled or consumed by humans[9].

It is thought that almost all human-to-human EBOV infections are due to direct contact with blood and/or body fluids (*e.g.*, saliva, mucus, vomit, feces, sweat, tears, breast milk, urine, and semen) from symptomatic/dead patients[7]. Thus, extreme care must be taken when handling the body fluids of patients with EVD to avoid infection[7]. Indeed, two thirds of the EVD cases in the Guinea epidemic during 2014 may have contacted the virus via unprotected (or unsuitably protected) contact with infected corpses during Guinean burial rituals.

7. Clinical features of EVD

EVD tends to cause the severest form of viral hemorrhagic fever in humans. Most EVD cases manifest as a sudden onset of influenza-like symptoms, such as high fever, chills, malaise, and myalgia[1,3,6,34], which may develop to systemic gastrointestinal symptoms (vomiting and diarrhea) and respiratory (chest pain and cough), vascular (conjunctival injection and edema), and neurological (headache, confusion, and coma) symptoms[1,3,6]. Hemorrhagic symptoms may follow, including petechiae, ecchymosis, and uncontrolled mucosal hemorrhage[1,3,6]. These symptoms can resemble other diseases however, such as malaria, cholera, typhoid fever, meningitis, and other viral hemorrhagic fevers. Cause of death is usually from multiple organ failure due to these complications[1,3,6].

General laboratory data are nonspecific to EVD[1,3,35]. In the early phase of the disease, leukocytopenia and lymphocytopenia may be evident in peripheral blood, and subsequent neutrophilia and thrombocytopenia are often seen[1,3]. In addition, elevation of ectopic enzymes such as aspartate transaminase and alanine aminotransferase is common[1,3]. Abnormalities may occur in the blood coagulation system, such as prolonged prothrombin and partial thrombin time. At the end stage, secondary bacterial infections such as pneumonia may develop[1,3]. In nonfatal cases, a high fever may continue for about 5 to 9 d, but symptoms improve around 7 to 10 days after onset[1,3,36]. At that time, a humoral antibody response may be noted.

There are no specific symptoms in the early stage of EVD; thus, laboratory confirmation is essential[1]. RT-PCR and/or immunological methods (ELISA) are generally used for detection, as with other viral infections[1].

8. Present status of therapeutic drug developments for EVD

At present, there is no approved definitive treatment, such as vaccines or anti-viral drugs, for EVD[3,34]. Therefore, symptomatic treatment methods including infusion of electrolyte and/or antibiotics are mainly used[1,3].

Two promising candidate vaccines against EVD have been reported to date. The US National Institute of Allergy and Infectious Diseases and GlaxoSmithKline have developed one candidate EVD vaccine, cAd3-ZEBOV[37]. The vaccine is a chimpanzee-derived adenovirus vector with an Ebola virus gene inserted. The second candidate, rVSV-ZEBOV, has been developed by the Public Health Agency of Canada in Winnipeg[38]. The availability of these drugs for clinical use is eagerly awaited.

The experimental drug ZMapp has been administered in 3 cases so far. It contains three monoclonal antibodies (mAbs) that are designed to neutralize EBOV[39]. The mAb cocktail binds to and neutralizes the GP protein of EBOV and has been shown to prevent infection in monkeys[39]. ZMapp was administered to 2 American EVD patients who were infected while treating EVD patients in Liberia during the recent epidemic[40], and both completely recovered from serious EVD; however, another Spanish patient treated with the same drug has died[40]. It is too early to tell how effective this experimental treatment will be.

Among the anti-viral drugs under development, a nucleic acid analog known as "favipiravir" may be applicable to the treatment of EVD[41]. This drug was originally developed as a treatment for influenza[41,42] and it inhibits the synthesis of viral RNA through the action of RNA-dependent RNA polymerase (RdRp) of influenza virus[42]. Some mechanisms of viral RNA synthesis are similar between EBOV and influenza viruses[43], so it is expected that the drug will have similar effects on the RNA synthesis of EBOV. Indeed, significant effects against EVD have been reported in mice[43]. We may therefore see favipiravir being tried clinically in the present EVD epidemic.

9. Conclusion

We have described current knowledge of EVD based on a review of the literature. With the knowledge we have thus far, it appears that it will be difficult to predict the extent and outcomes of EVD epidemics in the future. However, about 30 years ago, human immunodeficiency virus (HIV) infection suddenly emerged and spread throughout the world, and now, thanks to continuous efforts by the medical community, effective treatment methods against HIV infection are available, although the disease cannot yet be eradicated. EBOV and EVD are poorly understood at present, but there is hope that effective treatment methods to combat EVD will soon be developed.

Conflict of interest statement

We declare that we have no conflict of interest.

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