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Ebola Virus Disease: History, Epidemiology and Outbreaks

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Abstract Over the past 40 years, sporadic Ebola virus disease (EVD) outbreaks have occurred mostly in the central African region. In March 2014, an outbreak of EVD was recognized in Guinea which would become the most significant outbreak of haemorrhagic fever in Africa to date. The outbreak started in Guinea and rapidly spread to Liberia and Sierra Leone, claiming thousands of lives. Many questions still remain regarding the ecology of Ebola viruses, but it is believed that contact with infected bushmeat is an important risk factor for initial spill over of the virus into the human population. At present, there is still no registered prophylaxis or curative biologicals against EVD.

Keywords Ebola virus · Filovirus · Outbreak · West Africa · Guinea · Liberia · Sierra Leone · Viral haemorrhagic fever

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Introduction

Ebola virus disease (EVD), previously known as Ebola haemorrhagic fever, is a highly fatal haemorrhagic fever of humans and non-human primates [1]. Viral haemorrhagic fever (VHF) is an acute disease, usually with high mortality rate, and characterized by multisystem involvement and a tendency to destabilize the vascular system consequently leading to a variety of bleeding manifestations, hence the label of haemorrhagic fever. The term haemorrhagic fever is somewhat of a misnomer for EVD as the disease rather resembles fulminant septic shock and, patients most often succumb due to multiorgan failure and or hypovolemic shock with diarrhoea as a major feature rather than bleeding [1]. For EVD, the mortality rates for outbreaks documented have ranged between 25 and 90 %. For those that do survive the infection, convalescence is usually protracted [1]. Known causative agents of VHF in Africa belong to the *Arenaviridae* (Lassa and Lujo viruses), *Bunyaviridae* (Crimean-Congo haemorrhagic fever and Rift Valley fever viruses) and the *Filoviridae* (Ebola and Marburg viruses) families of viruses. Ebola virus disease is associated with infection with viruses belonging to the *Ebolavirus* genus of the *Filoviridae* family [2]. The latter also includes VHF-causing *Marburgvirus* and recently described *Cuevavirus* [2, 3]. The filoviruses are enveloped, filamentous, non-segmented single-stranded RNA viruses. To date, five distinct viral species have been ascribed to the *Ebolavirus* genus, namely *Zaire ebolavirus* (ZEBOV), *Sudan ebolavirus* (SEBOV), *Taï Forest ebolavirus* (TEBOV), *Reston ebolavirus* (REBOV) and *Bundibugyo ebolavirus* (BEBOV) [reviewed in 4]. These viruses vary in geographical expanse and in apparent virulence and pathogenicity in humans and non-human primates. Ebolaviruses belonging to the *Zaire ebolavirus* species (EBOV) have been associated with the highest fatality rates of the disease, whereas the SEBOV has caused four confirmed outbreaks with a median

of 50 % fatality rate [5–14, 15••, 16–19]. Bundibugyo virus (BDBV) is the most recent addition to the genus *Ebolavirus* and emerged in Uganda in 2007 [20–23]. The virus caused another small outbreak in the Democratic Republic of the Congo (DRC) in 2012 [24]. The fatality rate of BDBV averages at about 30 %. The Reston virus (RESTV), the only ebolavirus described outside the African continent, causes mild to asymptomatic infections in humans [25–31]. The Taï Forest virus (TAFV) has been associated with a single non-fatal human infection but is highly fatal in chimpanzees [32].

The existence of EVD has been known to man for about 40 years, but many aspects of its history continue to be shrouded in obscurity. Since the first report of an EVD outbreak in 1976 and prior to the outbreaks in 2014, only 2345 human cases have been laboratory confirmed, relating to 1546 deaths. Leading up to 2014, outbreaks of EVD were predominantly scattered over the central African region. Similar to other African haemorrhagic fever viruses, viruses belonging to the *Ebolavirus* genus are considered to be zoonotic. The discovery of the source of EVD outbreaks has been described by many as the "holy grail" of modern virology, and understanding its complex ecology is the topic of many scientific studies [33]. In addition, apart from being described as one of the most fatal diseases known to humankind, only second to rabies, no prophylaxis or curative biologicals are licenced for preventing or treating of EVD [34]. Patient management is founded only on palliative care and symptomatic and supportive treatment [1].

Here we provide a concise account of the history of EVD with a focus on the main features of outbreaks to date, views on the evolution of ebolaviruses and current knowledge regarding the natural history of the virus.

Natural EVD Outbreaks in Africa Prior to 2014

A total of 23 confirmed natural outbreaks of EVD occurred in Africa over a 38-year period from 1976 to 2013 (not including exported cases of EVD or laboratory acquired cases). These outbreaks have been sporadic, and affected countries have included Sudan, the Democratic Republic of the Congo (DRC), Côte-d'Ivoire (or Ivory Coast) and, since 2000, Uganda and the Republic of the Congo.

The first outbreaks of EVD were recorded in 1976. Two outbreaks were reported as they occurred simultaneously in southern Sudan and the northern region of the Democratic Republic of the Congo (DRC) (then Zaire) [5, 6, 17]. The source of the outbreak in Sudan was located in the town of Nzara and linked to an index case that worked in a cotton factory [17]. The outbreak lasted from June to November and involved 284 cases with a case fatality rate of 53 %. In September 1976, the index case of an outbreak of a similar haemorrhagic fever was reported from Yambuku, a small village located in northern DRC located about 800 km from Nzara [5]. A total of 318 cases of VHF were reported in just 2 months with the second highest case fatality rate reported for an Ebola outbreak to date of 88 %. These outbreaks were characterized by massive nosocomial transmission with a reported 27 % of cases receiving injections at the Yambuku hospital. At the Yambuku hospital, 11 of a health worker staff cohort of 17 died of EVD during this outbreak. During virological investigations following the DRC outbreak, a virus similar to the previously described VHF-causing Marburg virus, was isolated in cell culture [6]. The virus was dubbed Ebola virus (EBOV) by Peter Piot, a scientist from the Institute of Tropical Medicine in Antwerp, named for the 240-km-long Ebola River. Laboratory characterization of the viruses isolated during these outbreaks subsequently showed that the viruses from the two locations/outbreaks were antigenically, biochemically and virologically distinct and belonging to the *Zaire ebolavirus* and *Sudan ebolavirus* species [35].

In 1977, following these initial outbreaks, a retrospectively diagnosed case in a nine-year-old girl in the village of Tandala in the DRC was reported [7]. Recognition of the case led to further investigations that revealed 7 % seropositivity of villagers in the Tandala region, suggesting that virus transmission had occurred in the past as well and may be more common than anticipated. From July to October 1979, another outbreak of EVD was reported from Yambio (25 km from Nzara) in Sudan [18]. The outbreak affected 34 individuals with a case fatality rate of 65 %. The index case of this outbreak was also linked to the cotton factory in Nzara. Again, the propensity of the virus to spread in a hospital setting and amongst close family contacts was highlighted during investigations.

In 1994, EVD re-emerged after an apparent quiescent period of almost 15 years. Ebola virus disease was diagnosed as the cause of illness in a 34-year-old Swiss ethologist working in the Taï National Park in Côte-d'Ivoire (or Ivory Coast) studying chimpanzees [32]. In November 1994, a massive die-off of chimpanzees was noted, and some of the dead animals were subject to necropsy to determine the cause of death. Just over a week after the necropsies were performed, one of a team of three researchers fell ill. Determining the cause of illness resulted in the isolation of a novel virus [32]. The virus was unique from the viruses associated with the DRC and Sudan outbreaks. The virus was named the Côte-d'Ivoire ebolavirus, but was recently renamed as TAFV [2]. The patient's condition was resolved, and this remains the only report of TAFV infection in a human. The cause of death in the chimpanzees was also explored and evidence of TAFV infection confirmed in one of the carcasses [32]. The ecology and epidemiology of TAFV remain obscure. Given the indication of high pathogenicity of this virus in chimpanzees, it cannot be disregarded as a potential public health threat that may emerge with the confluence of environmental, behavioural and other factors that drive the emergence of these viruses.

Since 1994, an outbreak of EVD has been reported almost annually leading up to the massive outbreak of the disease in West Africa in 2014. In Gabon, four confirmed EVD outbreaks have been reported with case fatality rates of up to 82 %. The first outbreak which was reported in 1994 and 1995 was diagnosed retrospectively [9]. A yellow fever (YF) outbreak was reported in the area at that time, and cases of haemorrhagic fever were therefore ascribed to YF. It was upon further retrospective laboratory investigation on the clinically diagnosed YF cases that the co-circulation of EBOV was shown [9]. The outbreak appeared to originate from gold panning camps in the northeast Gabon located within a rain forest habitat. A total of 52 cases and 31 deaths were reported during this time. Again, the die-off in chimpanzee and gorilla populations in the affected area coincided with recognition of disease in humans. A second outbreak of EVD was reported in early 1996 also in the northeast Gabon. This outbreak was linked to the slaughtering of a chimpanzee found dead in the rain forest, ultimately involving 37 confirmed human cases with 21 fatalities [9]. The third epidemic also in mid-1996 involved 60 cases with a 74 % fatality rate. The index case was reportedly a forest hunter, and again, the outbreak coincided with the die-off in chimpanzee [9]. The most recent outbreak of EVD in Gabon was reported from October 2001 to March 2002 [10]. Again, the Ogooue'-Ivindo Province located in the northeast Gabon was affected. The outbreak also spilled over to adjacent Republic of the Congo. A total of 122 cases were reported from the two countries with 96 deaths (79 % case fatality rate). During this period, abnormally high levels of animals were found dead, including great apes and monkeys, in forests adjacent to the compounds where human cases were reported. Another unconfirmed EVD outbreak was reported in June 2002 affecting Gabon and Congo [10].

The DRC has been the country most often affected by EVD outbreaks. Apart from the 1976 and 1979 outbreaks, another five EVD outbreaks were recorded from 1995 to 2014. One of the largest and deadliest EVD outbreaks was recorded in 1995 in Kikwit. From January to July, a total of 315 cases were recorded with 250 deaths, 80 of those were health care workers [8, 36, 37]. Recognition of the outbreak was severely delayed with diagnosis of EVD only made in May 1995. This has become a feature of most EVD outbreaks to date. The outbreaks occur in locations where communities are typically ill served for even basic health care needs. In the absence of adequate hospital infrastructure, severe health care staff shortages and very limited access to laboratories it is understandable that public health surveillance for recognizing disease trends is problematic. Twelve years lapsed after the Kikwit outbreak before another outbreak of EVD erupted in the Kasai Occidental Province of the DRC in 2007 and again in 2008 [12, 13, 16]. In 2012, the DRC reported a small EVD outbreak associated with the circulation of BDBV involving 36 confirmed cases [24]. All other outbreaks in the DRC to date have been associated with EBOV. In August 2014, the World Health Organization announced an outbreak of EVD in the Equateur Province of the DRC. The outbreak was contained by November 2014, with a total of 66 cases reported. This outbreak was epidemiologically and virologically unrelated to the outbreak of EVD in Guinea, Sierra Leone and Liberia at the time [14].

From 2000, EVD outbreaks were also recorded in the Republic of the Congo and Uganda. The largest outbreak of EVD (before 2014) was reported in the north-central Uganda, Gulu district, from 2000 to 2001 caused by the Sudan virus (SUDV) [38]. It involved 425 cases with a lower case fatality rate of 53 %. Attendance and participation in burial ceremonies were reported as a major risk factor during this outbreak, and again, health care workers were at particular risk. In 2007, the first occurrence of BDBV was recorded in a milder outbreak of EVD involving 149 cases in the western Uganda [20, 21]. Three additional small outbreaks associated with SUDV were recorded in 2011 and two in 2012 involving only 17 cases (but 8 deaths) [22, 38]. Three highly fatal EVD outbreaks were reported in the Republic of the Congo from 2001 to 2003, with no further outbreaks reported since. The average case fatality rate during the three outbreaks exceeded 80 % and included the most fatal outbreak reported to date (case fatality rate of 89 %, 128 deaths of 143 cases). The first outbreak occurred with circulation of EBOV in the Congo and Gabon [5]. Thereafter, the disease reoccurred at the end of 2002 and again during the last months of 2003 [6].

2014 EVD Outbreak in West Africa

Before 2014, EVD outbreaks have been characterized in its occurrence only by its random nature, occurring after periods of apparent epidemiological silence and only rarely reoccurring in the same location [33]. EVD has been widely regarded as of low public health importance in Africa compared to the heavy burden inferred by infectious diseases such as malaria, tuberculosis and acquired immunodeficiency syndrome [39, 40]. In March 2014, the World Health Organization declared the emergence of EVD in Guinea, announcing what would become the most sizeable, fatal and protracted outbreak of EVD in recorded history [41]. As of 15 December 2014, a total of 18,464 suspected cases (with 11,699 confirmed cases) associated with 6841 deaths have been recorded spanning three countries in West Africa: Guinea, Liberia and Sierra Leone [42]. Although the outbreak originated in Guinea, the brunt of the outbreak has been borne in Liberia and Sierra Leone accounting for nearly 90 % of the cases recorded up to date [42]. On 8 August 2014, the World Health Organization declared the outbreak an international public health emergency and called for intensified multinational support for the containment of the outbreak [43]. Although the outbreak

is widely described as the "most fatal" outbreak of EVD to date, this is a reflection of the scale of the outbreak rather than the case fatality rate. This figure has fluctuated between 30 and 60 % in the past months and certainly will continue to fluctuate as the case counts are tallied and data verified [44].

The index case of the outbreak was likely a 2-year-old infant who died on 6 December 2013 [45••]. Several family members and a number of health care workers had contact with these family members. According to Baize et al., one of the affected health care workers triggered the spread of the virus to at least three districts of Guinea [45••]. The epidemiological curve of EVD cases in Guinea, after almost a year of circulation of virus in this country, has been characterized by multiple peaks and troughs most likely relating to the relative success of containment measures versus reintroduction of the virus from neighbouring affected areas in Liberia and Sierra Leone [41]. With a spike of cases in Guinea around March 2014, the first cases of EVD were reported in the Lofa district of Liberia (bordering on the affected districts of Guinea) with a rapid spread to the capital, Conakry. Likewise, in May, EVD spread to the districts of Kenema and Kailahun in Sierra Leone. From July onwards, the epidemic rapidly evolved to involve all the districts in all three countries, although certain hot spots of transmission persists in both countries [41]. Exportation of EVD cases outside of these countries (which is the subject of the next section) also started around this time.

Genetic characterization of virus isolates from Guinea and Sierra Leone has revealed that the epidemic is caused by EBOV [45••, 46••]. Isolates from Guinea and Sierra Leone are however distinct amongst isolates of EBOV analysed to date. This suggests the virus was not introduced into Guinea recently, but has in fact been evolving in segregation from other ebolaviruses. Gire et al. showed through molecular clocking analysis that divergence of the currently circulating EBOV was likely around 2004. This shows that the current outbreak is not caused by direct, real-time introduction from previously known endemic zones but that the virus has been circulating in its natural reservoir in West Africa for at least a decade. Despite the distinct character of the currently circulating EBOV in West Africa, the level of homology between this virus and isolates of EBOV from Gabon and the Democratic Republic of the Congo is 97 % [45••, 46••]. The conclusion is that the unprecedented nature of the ongoing epidemic in West Africa is in fact not ascribed to unique viral factors, i.e., increased virulence or transmissibility. This has also been echoed in clinical observation of patients and analysis of the development of the outbreak and has not changed over the years [41]. Concerns do however exist that the virus may, through sustained passage from human to human, adapt to become more virulent, although this does not appear to be the case [46••, 47].

It is widely recognized that the outbreak is being fuelled by socio-economic factors in the affected countries. The focus countries of this outbreak have been subject to civil war and upheaval in the recent history and are afflicted with low literacy rates and poor health and surveillance infrastructure [48]. Doctor Margaret Chan, the current Director-General of the World Health Organization summarizes the fuel behind the Ebola outbreak in West Africa in one word: "poverty" [48]. Poor health conditions are perpetuating the outbreak, spreading the disease to those that seek treatment in the poorly staffed and equipped facilities in these countries [41, 48, 49]. As reported in EVD outbreaks before, health care workers themselves are also often the victims of the outbreak, and at the time of this writing, more than 400 health care workers have succumbed to EVD during this outbreak alone. Also, as in previous outbreaks, the challenges associated with contact tracing which requires mobilization of the affected communities are well noted [41]. Conventional approaches for containment of haemorrhagic fever outbreaks are compounded by the massive scale of this current outbreak [41]. Ebola outbreaks before 2014 were typically reported from very rural and secluded locations. The current outbreak plays off against a backdrop of reasonable interconnectivity and mobility within the countries but also across porous borders. It is generally accepted that the outbreak is vastly underestimated. In Meltzer et al., the development of the outbreak is calculated through modelling at the hand of different levels of intervention. It is shown how delayed intervention contributes to the expansion and scale of the outbreak. In the worst-case scenario, upwards of a million cases could be expected by 2015 [50].

EVD Outbreaks Associated with Exported Cases and Laboratory Exposures

The EBOV has only been exported from endemic zones on singular occasions to date (see Table 1). Prior to 2014, EVD had only been exported to South Africa. The case involved a medical practitioner who was tending to EVD patients in Libreville during the Gabon outbreak in 1996 [51]. The practitioner travelled to South Africa for medical treatment for an acute febrile illness without disclosing his history of possible exposure. The patient was extensively investigated but recovered and was discharged without a diagnosis. When a nurse tending to the patient fell ill with a clinical picture compatible with haemorrhagic fever, a diagnosis of EVD was confirmed at the National Institute for Communicable Diseases in South Africa. Despite intensive following up more than 300 possible contacts of the two identified cases, no additional secondary cases were reported. Further exportation was reported since July 2014. The EBOV was exported to Senegal, Nigeria, Spain, the USA and Mali over the course of several months whilst the EVD outbreak was exploding in West Africa [52–58] (Table 1). The effectiveness of conventional containment measures involving case identification and isolation has

Table 1 Summary of exported EVD cases and laboratory-acquired EBOV infections

Year	History	Country affected	Total number of cases	Fatalities	Reference
1976	Laboratory worker accidentally inoculated via needle stick with infected clinical material. Treated with interferon and convalescent serum	UK	None	None	[59]
1996	Health care worker treated EVD cases during Gabon outbreak. Travelled to South Africa where hospitalized with EVD which was diagnosed retrospectively. A nurse contracted EVD whilst caring for this patient	South Africa	2	1	[51]
1996	Reported laboratory exposure in laboratory worker	Russia	1	1	[60]
2004	Laboratory worker accidentally inoculated via a needle stick whilst drawing blood from infected guinea pigs during vaccine trail	Russia	1	1	[61]
2014	Person infected in Liberia travels to Lagos where diagnosed with EVD. Sets of an outbreak of EVD that affects mostly health care workers	Nigeria	19	8	[61]
2014	Person from Guinea travels to Dakar where he dies of EVD	Senegal	1	1	[53]
2014	Priest diagnosed with EVD evacuated (second Spanish citizen to be evacuated for treatment to Madrid) from Sierra Leone to Spain for treatment in September 2014. Health care worker is infected in Spain	Spain	2	1	[54]
2014	Four patients with EVD evacuated to USA for treatment with no secondary cases recorded. In September 2014, man travels from Liberia to USA, developed signs and symptoms of EVD in the USA and was subsequently diagnosed. Two cases of secondary transmission detected in nurses. In October 2014 EVD was diagnosed in a medical worker returning from Guinea, at the time of this writing no secondary cases were associated with this case	United States of America	4	1	[55], [56]
2014	Two-year-old child from Guinea taken to Mali by family dies of EVD in Kayes. No secondary cases related to this case noted. In November 2014, nurse dies after treating Muslim Grand Imam from Guinea. Six additional cases recognized in family and health care worker contacts	Mali	7	6	[57], [58]

A number of other cases acquired in West Africa were evacuated to Europe and the USA for treatment, without further spread in those countries

been clearly demonstrated with containment of the outbreaks in Nigeria, Senegal and Spain at the time of this writing [52–54].

A total of three cases of laboratory-acquired ebolavirus infection have been reported in 38 years of recorded EVD history. All three incidents occurred in maximum containment facilities where workers were exposed to EBOV through needlestick injuries [59–61]. Another two cases of needlestick exposures to EBOV were reported in the USA and Germany whilst working under maximum containment conditions [62, 63].

The so-called Asian strain of ebolavirus, RESTV has been exported on numerous occasions through the translocation of cynomolgus monkeys from the Philippines [reviewed in 29, 64]. The first report of RESTV was during the quarantine of wild-caught cynomolgus monkeys (*Macaca fascicularis*) imported from the Philippines at an animal holding facility in Reston, Virginia, USA, in 1989 [23–25]. Some of the quarantined animals suffered from a highly fatal disease with similar features as simian haemorrhagic fever (indeed co-infection was established in some of the animals). An Ebola-like virus was isolated from these animals and on subsequent investigation found to be related but a distinct variant from the African strains [23]. The exportation of monkeys from the Philippines was associated with six similar outbreaks in cynomolgus monkeys reported in the USA, Italy and the Philippines. Interestingly, although highly fatal in cynomolgus monkeys (or Asian monkeys), and less virulent than EBOV and SUDV in this model, RESTV is thought to be apathogenic in humans and African monkeys [reviewed in 29].

Natural History of the Ebola Virus

Filoviruses have only been recorded in human history for the past 50 years; nevertheless, analysis of sequences of the filoviruses estimates the divergence from a common ancestor at approximately 10,000 years ago [65•]. A study by Carroll and co-workers estimates a common ancestor for RESTV and EBOV approximately 50 years ago and SUDV and Marburg

virus approximately 700 and 850 years ago, respectively [65•]. Despite the estimated ancient origin of these viruses, the source of EVD outbreaks has long evaded researchers with recent and mounting evidence for the reservoir of EBOV starting to provide pieces to the puzzle. The history and knowledge to date in this regard are extensively reviewed by Pourrut and Groseth and their co-workers [33, 66]. The zoonotic nature of EVD was appreciated early after recognition of the disease and the relation of the virus with Marburg virus which was a known zoonotic virus at that time. Outbreaks in human populations were often associated with reports of deaths in chimpanzee troops or contact with other dead-forest-dwelling animals (including gorillas and duiker antelope) [reviewed in 33]. The first evidence in this regard was made with the discovery of TAFV in 1994 [29] and then again very prominently during the Gabon outbreaks from 1996 to 2001 and the Republic of the Congo outbreaks [9, 10, 67]. Effects of EVD on gorilla populations are profound [67–69]. Between 2002 and 2003, it is estimated that up to 50 % of the gorilla population in the Lossi Sanctuary in the Republic of the Congo succumbed to the disease [67].

In several outbreaks, history of contact with bushmeat was reported for the identified index cases. For example, the index cases during the 1996 Gabon outbreaks involved, respectively, a group of children involved in butchering and carrying the carcass of a dead chimpanzee back to their village and a forest hunter [9, 67]. The bushmeat connection was also illustrated by Leroy and colleagues during the 2007 outbreak of EVD in the DRC. The putative index case bought freshly slaughtered bats from hunters for consumption [12]. In 2014, the EVD outbreak in DRC was once again drawn back to an index case involved in slaughtering of bushmeat before she fell ill [14].

Several studies have shown the connection of fruit bats and filoviruses [70, 71]. For example, bats were noted roosting in the cotton factory that was the centre of the Nzara outbreaks in 1976 and 1977 [17, 18]. In recent years, asymptomatic EBOV infection has been shown on several occasions in three species of fruit bat, *Hypsignathus monstrosus*, *Epomops franqueti* and *Myonycteris torquata* suggesting that these bats are true reservoirs of the virus [70, 71]. Subsequently, further evidence of EBOV circulating in these and additional species of fruit bats were shown in Ghana and Gabon [72, 73]. The seropositive *Eidolon helvum* fruit bat in Ghana was traced 13 months after initial sampling indicating long-term survival of a bat that was infected with EBOV in the past [74].

Many questions however remain. The maintenance and transmission of EBOV between bats, the possible routes of transmission to other forest-dwelling animals and perhaps the role of amplifying hosts remain elusive. In a study by Biek et al., the relationship between bats and EBOV appears to be recent and not a longstanding parallel evolution. The emergence of different genetic lineages is evident of multiple introductions of virus from the natural host, most likely bats, to susceptible wildlife and humans [75]. This begs the question if there is a primary reservoir species reintroducing the virus into bat populations, for example, through arthropods feeding on the bats. It is also notable that the evidence at hand has been focused on EBOV, and questions remain regarding the ecology of SUDV, TAFV and BDBV. Cynomolgus monkeys have often been associated with RESTV infection, but since the infection is highly lethal in this species, it does not satisfy the definition for reservoir species. The role of pigs as amplification host for RESTV has also been anticipated, but the question of bats as primary reservoir of this virus is still open [76, 77]. With many questions remaining regarding the ecology, epidemiology and clinical scope in humans, RESTV should not be underestimated as a potentially important pathogen in humans [78].

Conclusion

Compared to the contribution to the burden of infectious disease in African countries, EVD in the past has failed in comparison and was commonly considered as an obscure rarity affecting isolated populations. The outbreak affecting Guinea, Liberia and Sierra Leone has changed this view. This outbreak has not only highlighted the shortcomings in health care infrastructure and public health surveillance systems in Africa but also has placed this previously neglected disease onto the centre stage of world news. The gaps in knowledge regarding the natural ecology of this virus, transmission dynamics between individuals of the reservoir species and transmission strategies to achieve spill over to other species remain questions to be answered. The current outbreak in West Africa, but also recent studies involving pathogen discovery efforts in bats, suggests a wider than anticipated geographical spread of the ebolaviruses in Africa. Further studies to investigate and more fully understand the geographic expanse and reservoir species involvement are crucial to quantify risks of outbreaks in African countries. Further, the lack of specific therapeutics and preventative vaccines has also been scrutinized, and studies in this field have been expedited to hopefully provide a solution in the near future.

Compliance with Ethics Guidelines

Conflict of Interest All the authors have no conflict of interest to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Formenty P. Ebola virus disease. In: Ergönül O, Can F, Akova M, Madoff L (eds). Emerging infectious diseases, clinical case studies. Academic Press, 2014: 121–134. ISBN: 978-0-12-416975-3.
2. Kuhn JH, Boa Y, Bavari S, et al. Virus nomenclature below the species level: a standardized nomenclature for natural variants of viruses assigned to the family Filoviridae. Arch Virol. 2013;158: 301–11.
3. Negredo A, Palacios G, Vásquez-Morón S, et al. Discovery of an Ebolavirus-like filovirus in Europe. PLOS Path. 2011;7(10): e1002304.
4. Barrette RW, Xu L, Rowland JM, McIntosh MT. Current perspectives on the phylogeny of Filoviridae. Infect Genet Evol. 2011;11: 1514–9.
5. World Health Organization. Ebola haemorrhagic fever in Zaire, 1976. Bull World Health Organ. 1978;56:271–93.
6. Johnson K, Webb P, Lange J, Murphy F. Isolation and partial characterization of a new virus causing haemorrhagic fever in Zaire. Lancet. 1977;1:569–71.
7. Heymann DL, Weisfield JS, Webb PA, et al. Ebola hemorrhagic fever: Tandala, Zaire, 1977–1978. J Infect Dis. 1980;142(3):372–6.
8. Khan AS, Tshioko FK, Heymann DL, et al. The re-emergence of Ebola haemorrhagic fever, Democratic Republic of Congo, 1995. J Infect Dis. 1999;179:S76–86.
9. Goerges A-J, Leroy EM, Renaut AA, et al. Ebola haemorrhagic fever outbreaks in Gabon, 1994–1997: epidemiological and health control issues. J Infect Dis. 1999;179 Suppl 1:S65–75.
10. World Health Organization. Outbreak(s) of Ebola haemorrhagic fever, Congo and Gabon, October 2001-July 2002. Weekly Epidemiological Report. 2003;78(26):223–5.
11. Formenty P, Leroy EM, Epelboin A, et al. Detection of Ebola virus in oral fluid specimens during outbreaks of Ebola virus hemorrhagic fever in the Republic of Congo. Clin Infect Dis. 2006;42:1521–6.
12. Leroy EM, Epelboin A, Mondonge V, et al. Human Ebola outbreak resulting from direct exposure to fruit bats in Luebo, Democratic Republic of Congo, 2007. Vector-borne and Zoonotic Diseases. 2009;9(6):723–8.
13. World Health Organization. End of Ebola outbreak in the Democratic Republic of Congo. http://www.who.int/csr/don/2009_02_17/en/. (Accessed 17 December 2014).
14. World Health Organization. WHO declares end of Ebola outbreak in the Democratic Republic of Congo. http://www.who.int/mediacentre/news/statements/2014/drc-ends-ebola/en/. Accessed: 17 December 2014.
15. •• The World Health Organization Ebola Response Team. Ebola Virus Disease in West Africa – the first 9 months of the epidemic and forward projections. NEJM. 2014;371(16):1481–95. *A summary of the first nine months of the unprecedented outbreak of EVD in West Africa is summarized by key role players in the containment effort shedding light on the challenges and the vision forward for the containment of the outbreak.*
16. Muyembe-Tamfum JJ, Mulangu S, Kayembe JM, Kemp A, Paweska JT. Ebola virus outbreaks in Africa: past and present. Onderstepoort J Vet Res. 2012;79(2):451. doi:10.1402/ojvr.v79i2.451.
17. World Health Organization. Ebola haemorrhagic fever in Sudan, 1976. Bull World Health Organ. 1978;56:247–70.
18. Baron RC, McCormick JB, Zubeir OA. Ebola virus disease in southern Sudan: hospital dissemination and intrafamilial spread. Bull World Health Organ. 1983;61(6):997–1003.
19. Okware SI, Omaswa FG, Zaramba S, et al. An outbreak of Ebola in Uganda. Trop Med Int Health. 2002;7(12):1068–75.
20. Towner JS, Sealy TK, Khristova ML, et al. Newly discovered Ebola virus associated with hemorrhagic fever outbreak in Uganda. PLoS Pathog. 2008;4:e1000212.
21. Wamala JF, Lukwago L, Malimbo M, et al. Ebola hemorrhagic fever associated with novel virus strain, Uganda, 2007–2008. EID. 2010;16(7):1087–92.
22. Mbonye A, Wamala J, Kaboyo W, et al. Repeated outbreaks of viral haemorrhagic fevers in Uganda. Afr Health Sci. 2012;12(4):579–83.
23. MacNeil A, Farnon EC, Wamala J, et al. Proportion of deaths and clinical features in Bundibugyo Ebola virus infection. Uganda EID. 2010;16(12):1969–72.
24. Albarino CG, Shoemaker T, Khristova ML, et al. Genomic analysis of filoviruses associated with four viral hemorrhagic fever outbreaks in Uganda and the Democratic Republic of the Congo in 2012. Virol. 2013;442(2):97–100.
25. Ebola virus infection in imported primates—Virginia, 1989. MMWR 1989; 38(48): 831–2, 837–8
26. Jahrling PB, Geisbert TW, Dalgard DW, et al. Preliminary report: isolation of Ebola virus from monkeys imported to USA. Lancet. 1990;335(8688):502–5.
27. Update: filovirus infections among persons with occupational exposure to nonhuman primates. MMWR 1990; 39(16): 266–7; 237.
28. Miler RK, Baumgardner JY, Armstrong CN, et al. Update: filovirus infections in animal handlers. MMWR. 1990;39(13):221.
29. Morikawa S, Saijo M, Kurane I. Current knowledge on lower virulence of Reston Ebola virus (a review). Comp Immunol Microbiol Infect Dis. 2007;30:391–8.
30. Miranda ME, White ME, Dayrit MM, et al. Seroepidemiological study of filovirus related to Ebola in the Philippines. Lancet. 1991;337(3738):425–6.
31. Marsh GA, Haining J, Robinson R, et al. Ebola Reston virus infection of pigs: clinical significance and transmission potential. JID. 2011;204 Suppl 3:S804.
32. Formenty P, Hatz C, Le Guenno B, et al. Human infection due to Ebola virus, subtype Côte-d'Ivoire: clinical and biological presentation. J Infect Dis. 1999;179 Suppl 1:S48–53.
33. Pourrut X, Kumulungui B, Wittmann T, et al. The natural history of Ebola virus in Africa. Microbes Infect. 2005;7:1005–14.
34. Marzi A, Feldman H. Ebola virus vaccines: an overview of current approaches. Expert Rev Vaccines. 2014;13(4):521–31.
35. Richman DD, Cleveland PH, McCormick JB, et al. Antigenic analysis of strains of Ebola virus. Identification of two Ebola virus serotypes. J Infect Dis. 1983;147:268–71.
36. Bwaka MA, Bonnet MJ, Calain P, et al. Ebola hemorrhagic fever in Kikwit, Democratic Republic of Congo: clinical observations in 103 patients. J Infect Dis. 1999;179 Suppl 1:S1–7.
37. Guimard Y, Bwaka MA, Colebunders R, et al. Organization of patient care during the Ebola hemorrhagic fever epidemic in Kikwit, Democratic Republic of Congo, 1995. J Infect Dis. 1999;179(Suppl1):S268–73.
38. Shoemaker T, MacNeil A, Balinandi S, et al. Reemerging Sudan Ebola virus disease in Uganda, 2011. EID. 2002;18(9):1480–3.
39. Leroy EM, Gonzalez J-P, Baize S. Ebola and Marburg fever viruses: major scientific advances, but a relatively minor public health threat for Africa. Clin Microbiol Infect. 2011;17:964–76.
40. World Health Organization. Global health risks: mortality and burden of disease attributable to selected major risks. WHO, 2009. ISBN 978 92 4 156387 1

41. The World Health Organization. Ebola virus disease in West Africa—the first 9 months of the epidemic and forward projections. NEJM. 2014;371(16):1481–95.
42. Centers for Disease Control and Prevention. 2014 Ebola outbreak in West Africa—case counts. http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html (Accessed on 17 December 2014).
43. World Health Organization. WHO statement on the meeting of the International Health Regulations Emergency Committee regarding the 2014 Ebola outbreak in West Africa. http://www.who.int/mediacentre/news/statements/2014/ebola-20140808/en/. (Accessed 17 December 2014).
44. Kucharski AJ, Edmunds WJ. Case fatality rate for Ebola virus disease in west Africa. Lancet. 2014;384:1260.
45.•• Baize S, Pannetier D, Oestereich L, et al. Emergence of Zaire Ebola virus disease in Guinea—preliminary report. NEJM. 2014;371:1418–28. *The first study to provide molecular typing data for currently circulating EBOV in Guinea to show that EBOV as causative agent of the outbreak. The paper also summarizes the index case and early evolvement of EVD in Guinea*.
46.•• Gire SK, Goba A, Andersen KG, et al. Genomic surveillance elucidates virus origin and transmission during the 2014 outbreak. Science. 2014;345(6202):1369–72. *Gire et al. provides the first account after extensive full genomic sequencing analysis of currently circulating EBOV in Sierra Leone and Guinea. The study estimates the introduction of EBOV in Guinea*.
47. Dowall SD, Matthews DA, Garcia-Dorival I, et al. Elucidating variations in the nucleotide sequence of Ebola virus associated with increasing pathogenicity. Genome Biol. 2014;15:540.
48. Chan M. Ebola virus disease in West Africa—no early end to the outbreak. NEJM. 2014;371:1183–5.
49. Fauci AS. Ebola—underscoring the global disparities in health care resources. NEJM. 2014;371:1084–6.
50. Meltzer MI, Atkins CY, Santibanez S, et al. Estimating the future number of cases in the Ebola epidemic—Liberia and Sierra Leone 2014–2015. MMWR. 2014;63(3):1–14.
51. Richards GA, Murphy S, Jobson R, et al. Unexpected Ebola virus in a tertiary setting: clinical and epidemiological aspects. Crit Care Med. 2000;28(1):240–4.
52. Shuaib F, Gunnala R, Musa EO, et al. Ebola virus disease outbreak—Nigeria, July-September 2014. MMWR. 2014;63(39):867–72.
53. Mirkovic K, Thwing J, Diack PA. Importation and containment of Ebola virus disease—Senegal, August—September 2014. MMWR. 2014;63(639):873–4.
54. Parra JM, Samerón OJ, Velasco M. The first case of Ebola virus disease acquired outside of Africa. NEJM. 2014;371:2439–40.
55. Chevalier MS, Chung W, Smith J, et al. Ebola virus disease cluster in the United States—Dallas County, Texas, 2014. MMWR. 2014;63:1–3.
56. Centers for Disease Control and Prevention. Cases of Ebola diagnosed in the United States. http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/united-states-imported-case.html (Accessed 18 December 2014)
57. World Health Organization. Mali confirms its first case of Ebola. http://www.who.int/mediacentre/news/ebola/24-october-2014/en/ (Accessed 18 December 2014)
58. World Health Organization. Mali confirms two new cases of Ebola virus disease. http://www.who.int/mediacentre/news/ebola/25-november-2014-mali/en/ (Accessed 18 December 2014).
59. Emond RT, Evans B, Bowen ET, et al. A case of Ebola virus infection. Br Med J. 1977;2(6086):541–4.
60. Borisevich IV, Markin VA, Firsova IV, et al. Hemorrhagic (Marburg, Ebola, Lassa and Bolivian) fevers: epidemiology, clinical pictures and treatment. Problems in Virology. 2006;51(5):8–16 *[Russian]*.
61. Anonymous. Russian scientist dies after Ebola lab accident. Science 2004; 304 (5675): 1225.
62. Kortepeter MG, Martin JW, Rusnak JM, et al. Managing potential laboratory exposure to Ebola virus by using a patient biocontainment care unit. EID. 2008;14:881–7.
63. Gűnther S, Feldmann H, Geisbert TW, et al. Management of accidental exposure to Ebola virus in the biosafety level 4 laboratory, Hamburg. Germany JID. 2011;204 Suppl 3:S785.
64. World Health Organization. Viral haemorrhagic fever in imported monkeys. Weekly Epidemiological Record. 1992;67(24):183.
65.• Carroll SA, Towner JS, Sealy TK, et al. Molecular evolution of viruses of the family *Filoviridae* based on 97 whole-genome sequences. J Virol. 2013;87(5):2608–16. *Carroll and co-workers provide an important analysis of the relationship between Ebola and Marburg viruses, shedding light on the evolution of these viruses*.
66. Groseth A, Feldmann H, Strong JE. The ecology of Ebola viruses. Trends Microbiol. 2007;15(9):408–16.
67. Rouquet P, Froment J-M, Bermejo M, et al. Wild animal mortality monitoring and human Ebola outbreaks, Gabon and Republic of Congo, 2001–2003. EID 11(2): 283–290.
68. Leroy EM, Rouquet P, Formenty P, et al. Multiple Ebola virus transmission events and rapid decline of central African wildlife. Science. 2004;303(5656):387–90.
69. Whitfield J. Ape populations decimated by hunting and Ebola virus. Nature. 2003;422:551.
70. Leroy EM, Kumulungui B, Pourrut X, et al. Fruit bats as reservoirs of Ebola virus. Nature. 2007;438:575–6.
71. Pourrut X, Délicat A, Rollin PE, et al. Spatial and temporal patterns of Zaire ebolavirus antibody prevalence in the possible reservoir bat species. JID. 2007;196 Suppl 2:S176.
72. Hayman DTS, Yu M, Crameri G, et al. Ebola virus antibodies in fruit bats, Ghana, West Africa. EID. 2012;18(7):1207–09.
73. Pourrut X, Souris M, Towner JS, et al. Large serological survey showing cocirculation of Ebola and Marburg viruses in Gabonese bat populations, and a high seroprevalence of both viruses in Rousettus aegyptiacus. BMC Infect Dis. 2009;9:159.
74. Hayman DTS, Emmerich P, Yu M, et al. Long-term survival of an urban fruit bat seropositive for Ebola and Lagos bat viruses. PLoS One. 2010;5(8):e11978.
75. Biek R, Walsh PD, Leroy EM, et al. Recent common ancestry of Ebola Zaire virus found in a bat reservoir. PLOS Path. 2006;2(10):e90.
76. Marsh GA, Hainning J, Robinson R, et al. Ebola Reston infection in pigs: clinical significance and transmission potential. J Infect Dis. 2011;204 Suppl 3:S804–9.
77. Taniguchi A, Watanabe S, Masangkay JS, et al. Reston Ebolavirus antibodies in bats. Philippines EID. 2011;17(8):1559–60.
78. World Health Organization. WHO experts consultation on Ebola Reston pathogenicity in humans (WHO/HSE/EPR/2009.2). 2009; Geneva Switzerland.