

Ebola virus disease: societal challenges and new treatments

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Ebola virus disease (EVD) is a zoonotic disease that causes severe haemorrhagic fever, with high fatality rates of up to 90% in humans. Today, there is no effective treatment available. Person-to-person transmission occurs through exposure to blood or body fluids, which can threaten other household members and first-line healthcare workers. The first cases of EVD in Guinea were identified on 22

March 2014. It was initially believed that this like previous outbreaks would be self-limiting. However, lack of public health infrastructure, delays in virus detection and late implementation of control interventions contributed to widespread transmission of EVD in a region inexperienced in dealing with the disease. Socio-cultural and economic factors probably also played a key role in the spread of the disease, resulting in the current large-scale outbreak. Some promising candidate treatments for this disease are now being developed.

Keywords: ebola virus, outbreak, societal challenges, treatment, vaccine.

Emerging infectious diseases: a challenge to both human and veterinary health

Outbreaks of emerging infectious diseases continue to challenge both human and veterinary health worldwide. Events such as the outbreaks of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus, H5N1 avian influenza, Rift valley fever, foot and mouth disease and Crimean–Congo haemorrhagic fever virus in Europe and, recently, Ebola virus disease (EVD) in West Africa are just a few examples [1–6]. There are multiple causes of these epidemics, including factors such as increased population mobility, trade globalization and climate change potentially affecting the geographical distribution of viral vectors [7, 8]. The potential for bioterrorism through the deliberate release of an infectious agent in an area not previously affected has been raised and adds a further dimension to the emergence of infectious disease and its control. Zoonotic diseases caused by microorganisms whose principal reservoirs are wild and domestic animals are a leading cause of death and disease. In the past 60 years, more than 50% of emerging infectious diseases in humans have originated from zoonoses [9]. The zoonotic infection arena contains several billion humans, a growing number of domestic animals and many wild animals and vectors, which contribute to a large number of interactions between different players and zoonotic infections. Complex interactions between epidemiological,

ecological and social processes will promote the emergence and transmission of zoonotic diseases. The latest outbreak of EVD highlights the complexity of the interface between the elements mentioned above for zoonotic diseases. In this review, several crucial questions raised during the current outbreak will be discussed, such as: why EVD outbreaks occur in West Africa, far away from the endemic area; why this outbreak has occurred now; and which factors have contributed to the current widespread transmission of EVD, in contrast to all previous known outbreaks. In addition, the most promising candidate treatments will be summarized.

Filoviridae

The Filoviridae family belongs to the order Mononegavirales, but its members are significantly separated from other Mononegavirales on the basis of physiochemical, morphological, biological features and genomic structure [10]. Members of the Filoviridae are nonsegmented, RNA viruses with negative polarity [10]. These viruses are filamentous (as indicated by their name, derived from the Latin *filum* meaning ‘thread’). They form a thread-like shape, with a uniform diameter of about 80 nm [11] and a typical length of about 1200 nm [12, 13].

At present, Ebola Virus and Marburg virus are the only two recognized genera of the family Filoviridae. Lloviu virus (LLOV) can be classified as a

distinct genus, *Lloviu*, with one species, *Lloviu cuevavirus*. LLOV was recently detected in Schreiber's long-fingered bats (*Miniopterus schreibersii* Kuhl 1817), and phylogenetic analyses have demonstrated that LLOV is distant from both Marburg virus and EBOV [14, 15]. However, this virus has not yet been isolated. The genus Ebola virus (EBOV) contains the following species: Ebola virus, previously Ebola Zaire, Sudan Ebola virus, Reston Ebola virus, Tai Forest Ebola virus (formerly Côte d'Ivoire Ebola virus) and Bundibugyo Ebola virus [14, 15]. Within the genus Marburg virus, there is a single species, Marburg virus (formerly Lake Victoria Marburg virus), which consists of two very divergent 'viruses', Marburg virus and Ravn virus, which are approximately 20% divergent at the genetic level [14–16]. Of interest, this is in contrast to the known diversity for EBOV species, with a nucleotide difference between sequences of only 2.7%, 5.2% and 4.5% for EBOV, Sudan Ebola virus and Reston Ebola virus, respectively [16, 17]. Classification of the Filoviridae family will most probably continue to develop as further information becomes available through genome sequencing. Phylogenetic studies have been applied to estimate the age of filoviruses. The estimates of common ancestor age range from thousands to millions of years [18, 19], which indicates that these studies should be repeated using novel techniques and increased sample size to obtain more consistent estimates of the age of filoviruses. Recent studies of almost 100 whole-genome sequences using Bayesian coalescent phylogenetic analyses indicate nucleotide substitutions/site/year for different viruses ranging from 0.46×10^{-4} for Sudan Ebola virus to 8.21×10^{-4} for Reston Ebola virus. Studies by Carroll *et al.* [16] estimated recent common ancestry (approximately 50 years ago) for both Reston Ebola virus and EBOV.

The filovirus genome is approximately 19 kb in length. Filoviruses express seven different proteins [20]: nucleoprotein (NP), glycoprotein (GP), RNA-dependent RNA polymerase (RdRP) and the structural proteins virus protein (VP)24, VP30, VP35 and VP40. In addition, EBOV is able to express a truncated soluble GP through RNA editing and small soluble GP, which are secreted from the host cell [20, 21]. The surfaces of the viral membranes are spiked with GP trimers. These trimers are formed from GP1 and GP2 (product of cleavage of precursor GP). The GP trimers mediate receptor binding and are the target for neutralizing

antibodies. GP spikes, which embed on the virion surface, mediate virus entry [22, 23]. GP1 contains an excessively O-linked glycosylated mucin-like domain and a heavily N-linked glycosylated glycan cap domain, and these exterior domains are responsible for binding to a variety of host cell surface factors, as well as covering the receptor-binding domain under them [24]. NP and VP30 are required for RNA encapsidation [25, 26]. However, it has also been suggested that VP30 may act as a viral transcription activator [27, 28]. VP35 links NPs with the viral RdRP to construct the viral RNA synthesis complex for transcription and genome replication [29]. The VP35 protein is also known to interfere with interferon induction in both Marburg virus and EBOV [30, 31]. The matrix proteins VP40 and VP24 play essential roles in later steps of the replication cycle, such as assembly and budding [32–34]. VP 24 may also act as an interferon antagonist [35, 36]. It has been demonstrated that different forms of Ebola GPs can be released from infected cells and that these secreted GPs may activate noninfected dendritic cells and macrophages, causing massive release of pro- and anti-inflammatory cytokines and thereby affecting vascular permeability [37]. These GPs thus contribute to high virus pathogenicity. As mentioned above, EBOV is also able to express a truncated soluble GP, which contributes to a mechanism of host immune system evasion through absorption of antibodies and interference with antibody-mediated clearance [21, 38–40].

Ebola virus disease was first described in 1976 in Zaire [now the Democratic Republic of Congo (DRC)]. Since then, there have been multiple EBOV transmission events [41, 42] and several EVD outbreaks [43, 44]. In August 2014, the largest, most sustained and most widespread EVD outbreak in history became apparent and was declared a Public Health Emergency of International Concern by the World Health Organization (WHO). The WHO was notified of the outbreak in March 2014 [45], after a febrile illness cluster with high case fatality rate in the area of Gueckedou, Guinea. This attracted international attention and was subsequently identified as the viral zoonosis EBOV. Sequencing data showed that the 2014 outbreak in West Africa was due to infection with a strain of EBOV that differed from the viral strains identified in earlier outbreaks [45].

The suspected index case in the current outbreak is believed to be a 2-year-old boy in Guinea, who

died on 6 December 2013; it was initially suggested that he contracted the disease after exposure to an infected fruit bat [46]; however, new data indicate that EBOV transmission to this boy was instead through insectivorous bats [47]. His case became the starting point source for person-to-person spread of EVD into the population in several West African countries. Guinea, Liberia and Sierra Leone have been most affected, and these countries continue to report new cases. Since the beginning of this current outbreak, EBOV has infected 24 666 individuals and has caused 10 179 deaths, according to a WHO report issued on 18 March 2015 [48] (Fig. 1). However, the exact number of cases is difficult to determine, and the magnitude of the outbreak is believed to have been significantly under estimated. One case in Senegal was a traveller from Guinea, and a small number of cases in Nigeria and Mali originated from Liberia and Guinea, respectively. All these countries have since been declared free from EVD, largely as a result of rigorous control measures. There have also been a very few cases of EVD amongst travellers returning to Western Europe and the USA.

It is important to note that the symptoms, transmissibility, incubation period and death rate in the current outbreak are similar to those reported for

previous outbreaks. Genetic analysis of samples from the current outbreak suggests a single transmission event from the natural reservoir, followed by human-to-human transmission during the outbreak [49].

Clinical symptoms, transmission and infection control measures

Patients with EVD usually demonstrate clinical symptoms after an incubation period of 4–10 days, with a range of 2–21 days [20]. After a sudden onset of fever, vomiting, chills, myalgia and diarrhoea, the disease can evolve into a severe state with a rapid clinical decline. This disease phase is characterized by multisystem involvement and includes systemic, gastrointestinal, respiratory, vascular and neurological symptoms (Table 1). Haemorrhagic manifestations include petechiae, ecchymosis and mucosal haemorrhages. In later stages, patients demonstrate shock, convulsions and severe metabolic disturbances [20, 50]. Patients with fatal disease develop clinical signs early during infection and die typically between day 6 and 16 with hypovolaemic shock and multi-organ failure. Haemorrhages can be severe but are only present in fewer than half of all patients and in the current outbreaks have been observed in less than 30% of patients. In nonfatal cases, fever is present

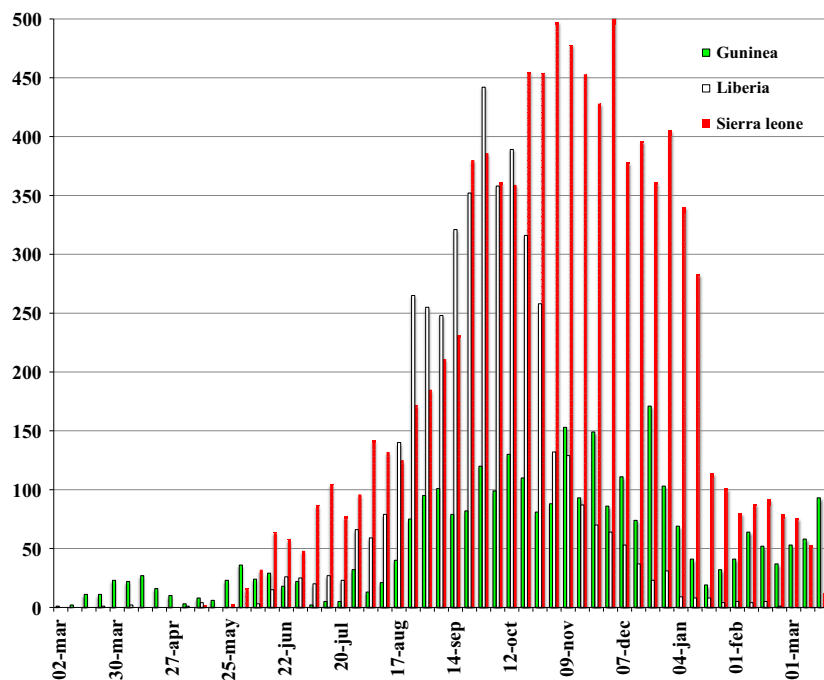


Fig. 1 The number of confirmed, probable and suspected cases of Ebola virus disease over time.

Table 1 Describing clinical symptoms related to the Ebola virus disease

Systemic symptoms	Prostration
Gastrointestinal symptoms	Anorexia, nausea, vomiting, abdominal pain, diarrhoea
Respiratory symptoms	Chest pain, shortness of breath, cough, nasal discharge
Vascular symptoms	Conjunctival injection, postural hypotension, oedema
Neurological symptoms	Headache, confusion, coma

for several days and patients typically improve around day 6–11, about the time that the humoral antibody response is noted [51]. The most common symptoms in the current outbreak are fever (87%), fatigue (76%), vomiting (68%), diarrhoea (66%), loss of appetite (65%), headache (53%), abdominal pain (44%) and myalgias (39%) [52]. Figure 2 shows the data from a previous study to prospectively determine whether body fluids contain EBOV RNA at different periods during the acute and convalescent phases [53].

Currently, it is unclear whether small droplets containing EBOV form within the human respiratory

tract in patients with EVD, even though EBOV particles have been found in human alveoli [54]. However, epidemiological data have clearly demonstrated that EBOV does not undergo traditional airborne transmission. The majority of patients in previous and current epidemics have been infected by direct contact [55, 56], and all EVD outbreaks in Africa have been contained without precautions against airborne transmission in the affected populations [57].

However, early experiments in nonhuman primates (NHPs) examining routes of infection of EBOV demonstrated that the virus could be aerosolized to small droplet or droplet nuclei size (mechanically) and cause lethal disease in rhesus macaques after inhalation of at least 400 pfu [58]. More recent experiments have shown that inhalation of less than 10 infectious particles of EBOV is sufficient to cause lethal disease in NHPs [59]. However, it is important to note that these studies do not address the question of whether EBOV is aerosolized naturally. Direct contact with body fluids from patients with EVD is the most likely way of transmitting EBOV. The evidence from previous and current outbreaks, epidemiological data and animal experiments all clearly demonstrate that contact with EBOV-infected fluids can lead to infection. Despite strong evidence to suggest that contact with body fluids is the route of EBOV transmission, it remains unclear when (i.e. how long postdisease onset) and which (e.g. sweat and tears) fluids contain infectious virus. In previous studies, EBOV has been isolated from blood,

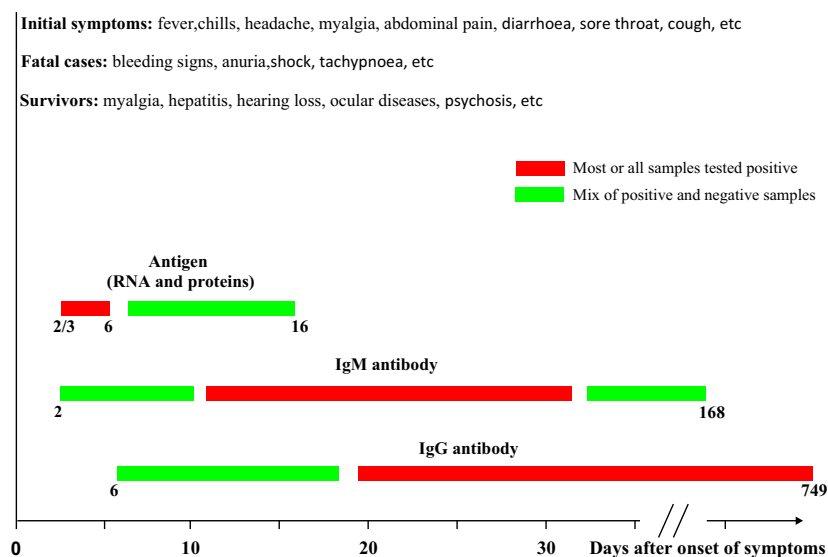


Fig. 2 Antigen and antibody responses amongst patients with Ebola virus disease. Under bars denote days after symptom onset.

saliva, breast milk and semen [60], whereas only viral RNA has been detected in sweat, tears, faeces and skin, rectal and vaginal swabs. It remains unclear how much infectious virus is secreted in different body fluids at different periods postdisease onset. Assessing the concentration of infectious virus during different time-points from disease onset in infected patients may help to determine when and how much virus is shed in different body fluids.

Very recent data from a 36-year-old male patient (treated in Hamburg, Germany) demonstrated high levels of viral RNA in plasma until 2 weeks after disease onset; RNA was also been detected in sweat until 40 days postdisease onset, whilst the level of viral RNA decreased below the detection level in urine at 31 days postonset [61].

As described above, EBOV is spread through direct contact with body fluids from an infected person and by contact with contaminated surfaces or equipment; therefore, patients with suspected or confirmed EVD should be isolated either in a isolation/specific room or a restricted area. Healthcare workers should also use dedicated equipment, which should be exclusively assigned to patient with EVD care areas. All healthcare workers and visitors should carry personal protective equipment (according to the expected level of risk, based on WHO recommendations and national/institutional guidelines) and hand hygiene should be performed (alcohol-based hand rub solution or soap and running water). Further details are available in the WHO and/or national regulations and recommendations [62].

Factors contributing to the magnitude of the current EVD outbreak

As mentioned above, the causative EBOV strain in this current outbreak is closely related to that in previous EBOV (Ebola Zaire) outbreaks in Central Africa [49]. However, by August 2014, the current outbreak had become the largest, most sustained and most widespread EVD outbreak in history. It has been suggested that EBOV could have been circulating in West Africa for about a decade [49], which raises the question of why there is an EVD outbreak in West Africa now. Another pressing issue concerns the factors that contributed to the current widespread transmission of EVD, in contrast to all previous known outbreaks which were limited in scope. The huge EVD epidemic in West Africa presents unique challenges because of

spread into crowded urban environments and occurrence in remote communities. One year after the first case of EVD in Guinea, it can be concluded that health teams at urban, county and district levels, particularly in rural counties with remote regions, need adequate training in: (i) case reporting, investigation and management, (ii) contact tracing, (iii) safe burial, and (iv) safe sample collection, processing and transport for diagnostic testing. Control of the epidemic is much more challenging in rural counties, as there are few roads, most of which are in poor condition, an overall lack of vehicles, no internet connectivity and limited telephone network coverage. Therefore, the development of novel communication and transportation network strategies for these remote communities is critical for management of EVD in such areas.

In general, the following three elements can be cited as crucial factors contributing to the current substantial and widespread outbreak in West Africa (Fig. 3): (i) delays in outbreak detection, (ii) lack of public health infrastructure, and (iii) socio-cultural factors.

Delays in outbreak detection

The suspected index case in the current outbreak, the 2-year-old boy in Guinea, contracted the disease and died at the end of 2013 [46]. However, the outbreak was not identified until March 2014 [45], which enabled several transmission chains to advance in the region and to cross its borders. A

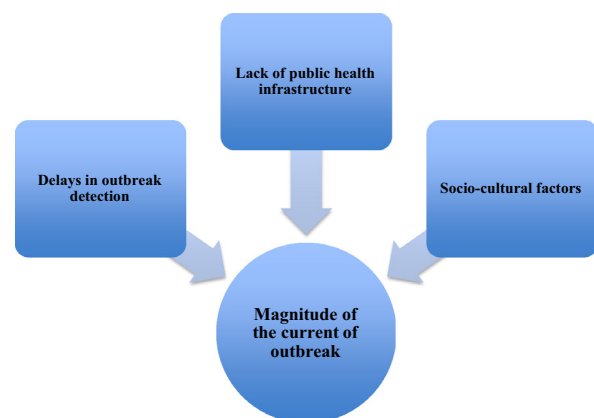


Fig. 3 Schematic representation of the most important factors contributing to the current and widespread outbreak of Ebola virus disease in West Africa.

number of factors impede the early identification of EVD outbreaks in Africa in general and in West Africa in particular. First, only a very few EVD outbreaks have occurred in Africa (East and Central Africa) since the first outbreak was identified in 1976, so awareness of the disease tends to be low. In addition, some areas at risk of EVD have not yet experienced an outbreak, which has strongly limited community-level knowledge of the disease [63]. Secondly, the early symptoms of EVD are nonspecific [64], which increases the likelihood of misdiagnosis. Thirdly, there is a lack of diagnostic testing in low-income countries. Fourthly, there is a lack of epidemiological monitoring for the timely identification of case clusters.

Lack of public health infrastructure

An insufficiency of resources at an early stage following outbreaks in the region is most probably the key factor responsible for the excessive scale of the ongoing EVD epidemic in West Africa [65]. In particular, the lack of sufficient quantities of essential supplies to implement infection control measures in healthcare settings and the low number of healthcare workers and staff available to manage a growing case burden contributed significantly to the widespread transmission of EVD in the current outbreak.

Socio-cultural factors

Socio-cultural and economic factors in the continent of Africa are a very important element contributing to the spread of infectious disease and also complicate the implementation of control interventions. Therefore, these factors have probably had a key role in the current EVD outbreak. In particular, cultural practices involving touching and washing the body of the deceased contribute to the dissemination of the EBOV. The associated potential for transmission to neighbouring and distant areas via exposed funeral attendants can facilitate the development of major epidemics [66]. Moreover, the lack of prior experience and knowledge of the disease can lead communities to deny its existence and to associate illness with witchcraft or an alleged government conspiracy to gain control of the population or attract resources from the international community [67]. For instance, during the ongoing epidemic in West Africa, a group of individuals looted equipment and potentially contaminated materials from an isolation facility in a quarantined neighbourhood. Finally,

the stigma carried by EVD survivors and the family members of EVD victims could exacerbate disease spread. In particular, uninformed families tend to hide relatives and friends infected with EVD, to avoid being shunned by their own communities, which enhances transmission rates. The problem is compounded by the high case fatality ratio of EVD, which leads misinformed communities to associate case isolation with a death sentence.

Therapeutic agents and vaccines

To date, there are no approved antiviral medicines or vaccines for EBOV. However, there are several candidate treatments with promising results *in vitro* and *in vivo*. Current research programmes for developing new therapeutic tools against EVD include the use of antibodies, plasma transfusions from convalescent patients, novel small-molecule antiviral agents and vaccines. The most promising medicines and vaccines available at present are summarized below (see Table 2).

Neutralizing antibody therapy

A neutralizing antibody targets the virus and inhibits virus replication at a very early stage of the replication cycle. Antibody-based EVD therapies are being developed using either convalescent serum from recovered patients or engineered monoclonal antibody (see below).

Transfusion therapy

The use of hyperimmune globulin has been well documented in other diseases (e.g. hepatitis B, rabies and varicella-zoster virus). In 1995, during an EVD outbreak in Kikwit, DRC, eight patients with EVD symptoms were treated with convalescent serum containing IgG EBOV antibodies from recovered patients with EVD. This treatment led to the survival of seven of these patients, a significantly improved survival rate compared with the average fatality rate of 80% in this particular outbreak [68]. However, it should be noted that these patients also received supportive treatment, and therefore, it is impossible to determine whether the serum transfusion was the crucial factor for patient survival [68]. The WHO has stated that blood or plasma transfusions from convalescent patients may be used for treatment of patients infected with EBOV in the current outbreak [69]. However, the use of transfusion therapy is complicated due to: (i) limited/nonexistent laboratory

Table 2 Antiviral and vaccine candidates to treat Ebola virus disease

Name (manufacturer)	Mechanism of action	Phase of development
ZMapp (Mapp Biopharmaceutical Inc)	Combination of three monoclonal antibodies	Phase 1
Brincidofovir (Chimerix)	Ebola: unknown CMV: incorporated into DNA chain, inhibiting DNA synthesis	Phase 1 (Ebola) Phase 3 (CMV and ADV)
Favipiravir (Fuji Film/ Toyama Chemical)	Nucleotide analogue that inhibits RNA Polymerases and causes lethal mutagenesis after incorporation into viral RNA3333	Phase 3 (influenza)
TKM-Ebola (Tekmira)	siRNA; interferes with proteins L, VP24 and VP35	Phase 1
AVI-7537 (Sarepta)	PMO, which inhibits protein VP24	Phase 1
BCX-4430 (Biocryst)	Nucleoside analogue	Preclinical
cAd3 (GSK/USNAIAD)	Stimulates immune response to Ebola glycoprotein using chimpanzee adenovirus	Phase 1
rVSV-Ebola (Newlink Genetics/PHAC)	Stimulates immune response to Ebola glycoprotein using rVSV	Phase 1

CMV, cytomegalovirus; ADV, adenovirus; VP, virus protein; siRNA, small interfering RNA; PMO, phosphorodiamidate morpholino oligomers; US NAIAD, National Institute of Allergy and Infectious Diseases; GSK, GlaxoSmithKline; PHAC, Public Health Agency of Canada.

infrastructure, (ii) lack of resources for safe collection and screening of blood from convalescent patients [70] and (iii) the requirement for a blood type match between donor and recipient. For these reasons, the use of plasma transfusion therapy is probably less promising than treatment with neutralizing monoclonal antibodies.

Monoclonal antibody treatment

The prototype product ZMapp is composed of three humanized monoclonal antibodies which target EBOV GPs. These antibodies have been chimerized by genetic engineering and manufactured in tobacco plants. The components of ZMapp are monoclonal antibody c13C6 from an existing antibody cocktail called MB-003 and two monoclonal antibodies (c2G4 and c4G7) from a different antibody cocktail, ZMab [71, 72]. Although it is still in the early phase of development, ZMapp has been used to treat seven patients with EVD, with five of those patients surviving [73]. However, there is a lack of adequate data about its safety and efficacy in animal models and in humans. In an early study involving EBOV in rhesus macaques, use of ZMapp produced promising results [72]. Nevertheless, there are still several barriers to the use of ZMapp for clinical treatment, for example the

manufacturer of ZMapp is not yet prepared for mass production and the product is still in the early phase of development. However, efforts are being made to scale up production [73].

Small-molecule (nucleoside analogue) antiviral agents

Brincidofovir (CMX-001)

This antiviral agent is an orally available lipid conjugate of cidofovir. Brincidofovir is being tested in early and late phase clinical trials for its effect on a number of viral diseases caused by different DNA viruses, including adenovirus, herpes viruses, orthopoxviruses, papillomavirus and polyomaviruses [74–76]. This drug has shown potent anti-EBOV activity at cell culture level and has also been used to treat patients with EVD. Brincidofovir has a long half-life, which means fewer doses and thereby fewer renal side effects compared with cidofovir [77]. However, there are currently no published data regarding the safety or efficacy of this molecule in treating EVD in either animal models or humans.

Favipiravir (T-705)

The pyrazinecarboxamide derivative favipiravir is a nucleotide analogue that inhibits the viral RdRP, either by interacting with and occupying

its catalytic domain or by incorporation into the newly synthesized viral RNA to cause lethal mutagenesis [78]. Favipiravir has primarily been studied for the treatment of influenza, but it has also demonstrated activity against arenaviruses and bunyaviruses [79–81]. Recent work demonstrated that this molecule inhibits the replication of EBOV in both cell culture and small animal models [82, 83]. Favipiravir could be administered orally [48, 81], which could prevent potential risks arising during drug injection. More importantly, phase III clinical trials of favipiravir for influenza treatment have been completed [84], making it possible for it to be quickly available for EVD therapy as long as anti-EBOV activity can be proved in NHP model.

Bcx-4430

This novel adenosine analogue has demonstrated efficacy in treating both EBOV and Marburg virus [85]. BCX-3340 indirectly inhibits RNA polymerase activity, resulting in termination of transcription and viral RNA replication. Preliminary data from animal experiments demonstrate very promising results.

Oligonucleotide-based antiviral agents

TKM-Ebola

This antiviral agent (intravenous formulation) is a small interfering RNA (siRNA) in early clinical trials [86]. This siRNA specifically recognize the RNA sequences of RdRP (EK-1), VP24 and VP35 and are packaged with polyethylenimine or lipid particles for *in vivo* delivery [86, 87].

Avi-6002

Another antisense oligonucleotide-based technology, termed phosphorodiamidate morpholino oligomers (PMOs), is also being applied for EVD therapy. These molecules inhibit viral replication by recognizing the specific single-stranded RNA or DNA of viruses and binding with them to form stable complexes [88]. The EBOV-specific PMO drug AVI-6002 is a mixture of positively charged PMOs targeting mRNA sequences of VP24 and VP35. Both TKM-Ebola and AVI-6002 have demonstrated promising *in vitro* and *in vivo* effects. However, there are two major issues to consider: (i) the mutation rate at the nucleic acid level is usually high for RNA viruses and this can lead to problems regarding genetic variation in the virus for antisense oligonucleotide-based drugs and (ii) both these molecules should be delivered into the cytoplasm more efficiently to reduce drug dosage and frequency.

Vaccines

At present, two vaccine candidates are receiving most of the attention in the research world. The first candidate is based on recombinant vesicular stomatitis virus (rVSV), which has been genetically engineered to invoke an immune response against EBOV GP [89, 90]. Newlink Genetics and the Public Health Agency of Canada are jointly developing this candidate vaccine [90], which has been named rVSV (rVSV-EBO). The second candidate, which is based on chimpanzee adenovirus serotype 3, is called chimpanzee adenovirus serotype 3 (cAd3-EBO) and is being jointly developed by Glaxo-SmithKline and the United States National Institute of Allergy and Infectious Diseases [91]. Both vaccine candidates have demonstrated very good efficacy in preventing EBOV infection in NHPs [92, 93].

rVSV-EBO

Vesicular stomatitis virus is a nonsegmented, negative-stranded RNA virus that is a member of the Rhabdoviridae family. Attenuated rVSV has been studied as a potential vector for several viruses, for example in the development of vaccines for the treatment of HIV, influenza and Marburg virus. rVSV-EBO has demonstrated efficacy for pre-exposure prophylaxis in small animal models and in NHP models.

cAd3-EBO

Recombinant adenovirus technology is the basis for this vaccine candidate. Initial studies using recombinant human adenovirus serotype 5 have generated promising results in animal models. However, widespread use is complicated by the fact that many adults are seropositive for Ad5, depending on country of origin. cAd3 is a rare adenovirus serotype, and therefore, humans do not have pre-existing immunity to it, which makes this serotype very interesting for developing new vaccine candidates. In a recent trial in chimpanzees, pre-exposure prophylaxis with cAd3 resulted in 100% protection. However, cAd3 has not yet been studied as a postexposure prophylaxis for EVD infection.

Conclusion

As illustrated above, there are several candidate treatments with promising results *in vitro* and *in vivo* as regards controlling EVD. It is hoped that some of these will soon be commercially available

to help treat patients who contract this devastating disease.

Conflict of interest statement

The author has no conflicts of interest to declare.

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