EBOLA: A REVIEW

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ABSTRACT:

Ebola virus disease (EVD) is a rare severe disease, often fatal, caused by the Ebola virus. It is transmitted through direct contact with blood or other bodily fluids (e.g. saliva, urine) from infected people, dead or alive. This includes unprotected sexual contact with patients up to seven weeks after they have recovered. Ebola virus does not transmit through the air as influenza does. After two days and up to 21 days following exposure to the virus, disease may start suddenly with fever, muscle aches, weakness, headache and sore throat. The next stage of disease is characterised by vomiting, diarrhoea, rash and failure of the liver and kidneys. Some patients also have heavy internal and external bleeding and multiorgan failure. There is no specific vaccine or treatment for the disease, but World Health Organization and other regulatory partners are currently working to identify potential viable treatments.

Key Words: Virus, Ebola, Diagnosis, Therapy

INTRODUCTION

Ebola, previously known as Ebola hemorrhagic fever, is a rare and deadly disease caused by infection with one of the Ebola virus species. Ebola can cause disease in humans nonhuman and primates (monkeys, gorillas. and chimpanzees) (Centre for Disease Control and Prevention; updated as of 27 Mar 2015). Ebola belongs to the family filoviridae. Term Filoviridae, taken from the Latin word "filum," meaning thread-like, based upon their filamentous structure. family *Filoviridae* consists of three The genera, Ebola, Marburg and Cuevavirus. Ebola and Marburg viruses are among the most virulent pathogens in humans (Feldmann and Giesbert, 2011). In the past, Ebola and Marburg viruses were classified as "hemorrhagic fever viruses", based upon their clinical manifestations, which include coagulation defects, bleeding, and shock. However, the term "hemorrhagic fever" is no longer used to refer to Ebola virus disease since only a small percentage Ebola patients actually develop of significant hemorrhage, and it usually occurs in terminal phase of fatal illness,

when the individual is already in shock (Bray, 2005; Mahanty and Bray, 2004).

Genus Ebola is divided into five identified species, four of which have caused disease in humans: Ebola virus (Zaire ebolavirus); Sudan virus (Sudan ebolavirus); Taï Forest virus (Taï Forest ebolavirus. formerly Côte d'Ivoire ebolavirus): and Bundibugyo virus (Bundibugyo ebolavirus). The fifth, Reston virus (Reston ebolavirus), has caused disease in nonhuman primates but not in humans (Centre for Disease Control and Prevention; updated as of 27 Mar 2015).

VIRION MORPHOLOGY, SIZE AND STRUCTURE

Ebola virions are enveloped, helical, cross-striated nucleocapsid, filamentous or pleomorphic that are flexible with extensive branching and are 80 nm in diameter and 970-1200 nm in length. In the center of the particle is the viral nucleocapsid which consists of the linear, negative sense, helical ssRNA genome wrapped about the NP, VP35, VP30 and L proteins. This structure is then surrounded by an outer viral envelope derived from the host cell membrane that is studded with 10 nm long viral glycoprotein (GP) spikes. Between the capsid and envelope are viral proteins VP40 and VP24.The genome of each virion is around 19kb in length, and codes for seven structural and one non-structural proteins. The gene order is as follows: 3' – leader – NP – VP35 – VP40 – GP/sGP – VP30 – VP24 – L – trailer – 5'. (Crary *et al.*, 2003)

PHYSICO-CHEMICAL PROPERTIES

Ebola virions are stable at room temperature and can resist desiccation. They get inactivated by soap, machine washing at high temperature and heating at 60°C for 30 minutes. Infectivity of virions greatly reduced or destroyed by UV light (including sunlight) and gamma irradiation, lipid solvents. β -propiolactone, formaldehyde, sodium hypochlorite, and Virus phenolic disinfectants. is not inactivated by freezing or refrigeration (Health Protection Service Centre; updated as of 22 Jan 2015).

EPIDEMIOLOGY

The virus family filoviridae came existence in 1967, when the into commercial laboratory workers with a severe and unusual disease were admitted to a hospital in Marburg, Germany. Further investigation led to the isolation and identification of the immediate source of the virus (Marburg virus) as green monkeys imported from Africa for use in research and vaccine production. The monkeys were euthanatized and the epidemic was contained with only 31 human cases and one generation of secondary transmission to health care workers and family members (DeMarcus et al., 1999; Peters and Leduc, 1999).

The Zaire Ebolavirus (causative agent of major outbreaks of hemorrhagic fever) was first discovered in 1976 near Ebola River in Zaire what is now the Democratic Republic of the Congo (Centre for Disease Control and Prevention; updated as of 27 Mar 2015). The traditional methods of quarantine like segregation of patients as well as closure of medical facilities to eliminate the major center for dissemination of infection through the use of unsterilized needles and syringes and the lack of barrier-nursing techniques ceased the transmission of highly virulent epidemic (Pattyn, 1978). The *Zaire virus*, since its first recognition in 1976, has caused multiple large outbreaks in Central Africa, with mortality rates ranging from 55 to 88 percent (WHO Ebola Response Team, 2014).

The Sudan ebolavirus has been associated with a case-fatality rate of approximately 50 percent in four epidemics: two in Sudan in the 1970s, one in Uganda in 2000, and another in Sudan in 2004 (Sanchej et al., 2004; Onyango et al., 2004; Ebola haemorrhagic fever in Sudan, WHO Report 1976). The research efforts that arose in response to the outbreak also quickly dwindled when the only convincing evidence that Ebola virus infections were continuing among humans consisted of a small outbreak in the Sudan in 1979 (Baron et al., 1983) and 1 case in Tandala, DRC, in 1977 (Heymann et al., 1980).

The Ivory Coast ebolavirus has only been identified as the cause of illness in one person, and that individual survived. The exposure occurred when an ethologist performed a necropsy on a chimpanzee found dead in the Tai Forest, where marked reductions in the great ape population had been observed (Formenty et al., 1999). The Bundibuqyo virus emerged in Uganda in 2007, causing an outbreak of Ebola virus disease with a lower case-fatality rate (approximately 30%) than is typical for the Zaire and Sudan viruses. Sequencing has shown that the agent is most closely related to the Ivory Coast species (Towner et al., 2008).

Fifth Ebola species, Reston virus, differs markedly from the others, because it is apparently maintained in an animal reservoir in the Philippines and has not been found in Africa (Jahrling, et al., 1990; Miranda et al., 1999). The Reston virus is known to cause disease only in non-human primates. It was first appeared in monkeys imported into a Reston, Virginia, primate facility outside of Washington DC, in 1989. Epidemics in cynomolgus monkeys (Macaca fascicularis) occurred in this facility and others through 1992 and recurred in 1996. Epidemiologic studies successfully traced the virus introductions to one Philippine exporter but failed to detect the actual

source of the virus. Nothing further was heard of the Reston virus until 2008, when the investigation of an outbreak of disease in pigs in the Philippines unexpectedly revealed that some of the sick animals were infected both by an arterivirus (porcine reproductive and respiratory disease virus) and by Ebola Reston virus. Serologic studies have shown that a small percentage Philippine pig farmers have IgG of antibodies against the agent without ever developing severe symptoms, providing additional evidence that Ebola Reston virus is able to cause mild or asymptomatic infection in humans (Barrette et al., 2009).

VIRAL RESERVOIRS

Perhaps the greatest mysteries regarding the filoviruses are the identity of their natural reservoir(s) and the mode of transmission to wild apes and humans (Bray, 2002; Pourrut et al., 2005). While Marburg virus has been isolated directly from bats captured in Uganda (Towner et al., 2009), only Ebola virus sequences, not infectious virus, have been detected in samples collected from bats in Central Africa (Leroy et al., 2005, Biek et al., 2006). However, studies suggest that bats are at least one of the reservoir hosts of Ebola viruses in Africa (Leroy et al., 2007). The transmission pathway from bats to humans, and the possible role of bats in the initiation of the 2014-2015 West African outbreak have not been defined. Filoviruses can latently or chronically infect their natural reservoir hosts. Primates seem to be susceptible hosts and non-human primates may even provide a frequent link to humans. They are unlikely however to be the true reservoir hosts, given the high pathogenicity of Filoviruses for African macaques, chimpanzees and perhaps great apes (Peters and Leduc, 1997).

The Kikwit epidemic, in 1995, also provided the opportunity to search for the elusive reservoir of Ebola virus in connection with an acute outbreak. The implicated index case was a charcoal maker who lived in the city of Kikwit He rode his bicycle through the savanna to an area of secondary forest, where he had exposure to tree-top, ground-level, and burrowing and animals. species of plants То complicate matters, he also had a small agricultural plot near a primary forest in a clearing near a stream. A decision was made to throw a wide net and capture arthropods and vertebrates from several biotopes, recognizing that the diversity of tropical species would be a limiting factor. Unfortunately, no evidence of ebola or antibodies reactive with the virus were found in vertebrates, and Ebola genomes were not amplified from the extensive arthropod collections. (Health Protection Service Centre; updated as of 22 Jan 2015).

Because the natural reservoir of Ebola virus has not yet been identified, the way in which the virus first appears in a human at the start of an outbreak is unknown. However, researchers believe that the first patient becomes infected through contact with an infected animal, such as a fruit bat or nonhuman primate.

TRANSMISSION

When an infection does occur in humans, the virus can be spread in several ways to others:

- Direct exposure to the blood, bodily fluids, of a dead or living infected person or animal
- Injury from needles and other sharp implements contaminated by the blood of a dead or living infected person or animal
- Direct exposure through broken • skin or mucous membranes (e.g. in mouth. under evelids) the to areas/items that have become contaminated with an Ebola patient's infectious fluids such as soiled clothing, bed linen, or used needles.
- Contact with bodily fluids includes unprotected sexual contact with patients up to seven weeks after they have recovered.

Ebola is not transmitted by the casual contact in public places with people that do not appear to be sick, handling money and groceries, by mosquitoes or other insects, through the air or by water, or in general, by food. Ebola viruses can survive in liquid or dried material for a number of days (this is a greater risk in healthcare facilities than in the community unless the area around a person with Ebola virus disease has been contaminated) (Crary *et al.*, 2003).

INCUBATION PERIOD

Generally, the abrupt onset of symptoms follows an incubation period of 2-21 days (World Health Organization; updated as of Sept 2014).

SIGNS AND SYMPTOMS

- Abrupt onset of fever and chills with myalgia, malaise, and headache
- Multisystem involvement follows that includes prostration; nausea, vomiting, abdominal pain, diarrhoea and pancreatitis; chest pain, cough, and pharyngitis; vascular and neurologic manifestations.
- Around Day 5, most patients develop a maculopapular rash that is prominent on the trunk followed by desquamation in survivors.
- Central nervous system involvement is often manifested by somnolence, delirium, or coma. Wasting becomes evident later, and bleeding manifestations, such as petechiaeand haemorrhage, occur in half or more of the patients.
- During second week, the patient defervesce and improves markedly or dies in shock with multi-organ dysfunction, often accompanied by disseminated intravascular coagulation, anuria, and liver failure.
- Convalescence may be protracted and accompanied by arthralgia, orchitis, recurrent hepatitis, transverse myelitis, psychosocial disturbances, or uveitis (Centre for Disease Control and Prevention; updated as of 27 Mar 2015).

DIAGNOSIS

Diagnosing Ebola in an individual who has been infected for only a few days is difficult because the early symptoms, such as fever, are nonspecific to Ebola virus infection and are seen often in patients with more common diseases, such as malaria and typhoid fever (Centre for Disease Control and Prevention; updated as of 27 Mar 2015).

However, if a person has early symptoms of Ebola and there is reason to believe that Ebola should be considered, the patient should be isolated and public health professionals notified. Samples from the patient can then be collected and tested to confirm infection. The incubation period (the time from infection with the virus to the onset of symptoms) for Ebola Virus Disease (EVD) is 2-21 days.

Ebola virus is detected in blood only after onset of symptoms, most notably fever. which accompany the rise in circulating virus within the patient's body. It may take up to three days after symptoms start for the virus to reach detectable levels. If specimens are collected less than 3 days after onset of symptoms, additional specimens will be needed if the test result on first specimen is negative. The second specimen should be collected at least 48 hours after the first specimen. Whole blood for serological testing can be collected after 8 days of onset of symptoms with strict infection prevention and control measures adhered to throughout process, including waste disposal and disinfection (World Health Organization; updated as of 19 Sept 2014).

Following specimens are collected for the diagnosis of EVD:

- Whole blood in EDTA (a minimum volume of 4mL), collected in plastic tubes from live patients;
- Oral swabs stored in a universal transport medium, collected from deceased patients or in situations where blood collection is not Swab possible children. e.g. collection from live patients is not recommended due to lower sensitivity for reverse transcription polymerase chain reaction (RT PCR) and antigen detection.
- For early detection of Ebola virus in suspect or probable cases, detection of viral RNA or viral antigen are the recommended tests.
- Laboratory-confirmed cases must test positive for the presence of the

Ebola virus, either by detection of virus RNA by RT-PCR, and/or by detection of Ebola antigen by a specific Antigen detection test, and/or by detection of Immunoglobulin M (IgM) antibodies directed against Ebola. • Two negative RT PCR test results, at least 48 hours apart, are required for a clinically asymptomatic patient to be discharged from hospital (World Health Organization; updated as of 19 Sept 2014).

Table1: Laboratory tests used in diagnosis	
Timeline of Infection	Diagnostic tests available
Within a few days after symptoms	Antigen-capture enzyme-linked
begin	immunosorbent assay (ELISA)
	testing
	IgM ELISA
	Polymerase chain reaction (PCR
	Virus isolation
Later in disease course or after	IgM and IgG antibodies
recovery	
Retrospectively in deceased patients	Immunohistochemistry testing
	PCR
	Virus isolation

Prevention

- Practice careful hygiene. For example, wash your hands with soap and water or an alcohol-based hand sanitizer and avoid contact with blood and body fluids.
- Do not handle items that may have come in contact with an infected person's blood or body fluids (such as clothes, bedding, needles, and medical equipment).
- Avoid funeral or burial rituals that require handling the body of someone who has died from Ebola.
- Avoid contact with bats and nonhuman primates or blood, fluids, and raw meat prepared from these animals.
- Avoid facilities in places where Ebola patients are being treated.
- After return from an infected place, monitor your health for 21 days and seek medical care immediately if you develop symptoms of Ebola.

- Healthcare workers who may be exposed to people with Ebola should follow these steps:
- Wear appropriate PPE.
- Practice proper infection control and sterilization measures.
- Isolate patients with Ebola from other patients.
- Avoid direct contact with the bodies of people who have died from Ebola.
- Notify health officials if you have had direct contact with the blood or body fluids, such as but not limited to, faeces, saliva, urine, vomit, and semen of a person who is sick with Ebola. The virus can enter the body through broken skin or unprotected mucous membranes in, for example, the eyes, nose, or mouth (Centre for Disease Control and Prevention; updated as of 27 Mar 2015).

THERAPEUTICS AND VACCINES

Till date, there are no vaccines to protect against EVD licensed for use in humans. Several vaccine candidates for the treatment are in development pipeline.

Of all, two most advanced vaccines identified are - based on recombinant vesicular stomatitis virus expressing an Ebola virus protein (VSV-EBOV) and chimpanzee adenovirus recombinant expressing an Ebola virus protein (ChAd-EBOV).rVSV-ZEBOV is being developed by NewLink Genetics and Merck Vaccines USA, in collaboration with the Public Health Agency of Canada while ChAd-EBOV is being developed by GlaxoSmithKline, in collaboration with the United States National Institute of Allergy and Infectious Diseases, Both vaccines have shown to be safe and efficacious in animals. (World Health Organisation; updated as of 17 Mar 2015).

Johnson & Johnson, in association with Bavarian Nordic, are developing 2-dose vaccination approaches for Ebola using different vaccines for the first and second approach is known doses. This as heterologous prime-boost. The two vaccine candidates are known as Ad26-EBOV and MVA-EBOV. Novavax, a biotech company, is developing a recombinant protein Ebola vaccine candidate based on the Guinea 2014 Ebola virus strain. The Russian Federal Ministry of Health is developing a recombinant influenza candidate Ebola vaccine, as well as other approaches. The recombinant influenza candidate is scheduled to start Phase I trials in the second half of 2015. Other products in development include an oral adenovirus platform (Vaxart), an alternative vesicular candidate stomatitis virus (Profectus Biosciences), an alternative recombinant protein (Protein Sciences), a DNA vaccine (Inovia) and a recombinant rabies vaccine (Jefferson University) (World Health Organization; updated as of 17 Mar 2015).

Transfusion of convalescent whole blood and plasma has been prioritized for use as an investigational therapy. Convalescent whole blood donated by EVD recovered patients is currently being administered in some Ebola treatment centres in Sierra Leone. Trials using convalescent plasma are underway in Liberia and in planning phase for Guinea (World Health Organization; updated as of 17 Mar 2015).

DRUGS AND MEDICINES

Many pre-existing medicines were considered for re-purposing to treat Ebola. Some are either being tested or considered for testing in patients with EVD or have already been used in patients with EVD. Several therapies have also been considered for use in treatment, but have been deemed appropriate to not be for further investigation. These drugs have been evaluated by the WHO Science and Advisorv Technical Committee on Emergency Ebola Interventions (STAC-EE) and categorized as follows:

- Drugs already under evaluation in formal clinical trials in West Africa. These include favipiravir and brincidofovir.
- Drugs that have been prioritized for testing in human efficacy trials, but for which such trials are not yet underway. These trials may include the following: Zmapp, TKM-100802, AVI-7537, BCX-4430, and interferons.
- Drugs that have already been given to patients for compassionate reasons or in ad hoc trials, including: Zmab; amiodarone; irbesartan + atorvastatin +/- clomiphene; and FX06.
- Drugs that demonstrate promising anit-Ebola activity in-vitro or in mouse models, but for which additional data should be generated prior to proceeding to clinical trials. These include: azithromycin; chloroquine; erlotinib/sunitinib; sertraline; and clomiphene.
- Drugs that had been prioritized or considered for prioritization and have now been deprioritized based on new data or more detailed analysis of old data. There is a single drug in this category, namely toremiphene (World Health Organization; updated as of 17 Mar 2015)

CONCLUSION

Ebolavirus causes an acute, serious illness which is often fatal if untreated.

Since its discovery in 1976 in a village near ebola, latest outbreak in 2014 in West Africa is the largest and most complex Ebola outbreak. There have been more cases and deaths in this outbreak than all others combined. It has also spread between countries starting in Guinea then spreading across land borders to Sierra Leone and Liberia, by air (1 traveller only) to Nigeria, and by land (1 traveller) to Senegal. Ebolavirus spreads through human-to-human transmission via direct contact (through broken skin or mucous membranes) with the blood, secretions, organs or other bodily fluids of infected people, and with surfaces and materials (e.g. bedding, clothing) contaminated with these fluids. Effective outbreak control includes seeking better ways to diagnose and treat Ebola infections, and using applied research to develop diagnostics, vaccines, and therapeutics. Raising awareness of risk factors for *Ebola* infection and protective measures that individuals can take is an effective way to reduce human transmission.

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