REVIEW

West Africa Ebola Outbreak 2014

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Ebola is caused by Ebola viruses (EBOV), members of the group of haemorrhagic fevers and it is one of the most dangerous infection diseases with mortality rates up to 90%. Ebola was firstly described in 1976 and since then occurred sporadically in Central Africa. Till 2014, more than twenty outbreaks were described, but number of deaths not exceeding 300 per outbreak. In 2014 came West Africa Ebola outbreak and the changeover appeared in Ebola epidemiology. During 2014 Ebola virus disease crossed the borders, affected five countries and number of cases and victims increased thousand times. The World is at attention and some countries have declared special rules for travellers from affected areas. This review aims to provide an overview of history of Ebola virus disease outbreaks, with the emphasis on 2014 West Africa Ebola outbreak.

Keywords: Ebola viruses; 2014; West Africa Ebola outbreak

1. Introduction

Ebola virus disease (EVD) is a sporadically occurring and high mortality disease caused by Ebola viruses (EBOV). There are five closely related strains of Ebola viruses. Four of them commonly cause disease in humans: Ebola virus (ZEBOV, formally known as Zaire); Sudan virus (SUDV); Tai Forest or Côte d'Ivoire virus (TAFV); and Bundibugyo virus (BDBV). The fifth, Reston virus (RESTV), has been caused disease only in nonhuman primates (monkeys, gorillas, and chimpanzees) [1, 2].

EBOV together with Marburg and Lloviu viruses make up the filoviruses family. All of the members of Filoviridae have similarities in the structure of virion, genome formation and most of them cause fatal haemorrhagic fevers in humans [3]. The illness included symptoms such as fever, headache, and malaise at onset, with profuse vomiting and diarrhea occurring 2-4 days later, haemorrhagic symptoms occur in severe cases. Ebola is one of the most lethal diseases. Mortality rate ranges from 53-88%. Ebola viruses are endemic to Africa and to the Philippines. Due to fact that Ebola is highly pathogenic disease with such as high mortality, must be conducted in a Biosafety Level 4 laboratory (together with Marburg virus, Lassa virus, Crimean-Congo haemorrhagic fever and various other haemorrhagic diseases).

EVD was firstly described in 1976 during two concurrent outbreaks [4, 5]. It was given the name 'Ebola' after the small river near the catholic mission of Yambuku, the epicentre of the 1976 Ebola haemorrhagic fever outbreak [13]. Between 1976 and 2014 twenty-four epidemics of EVD were verified, mostly caused by ZEBOV in Equatorial Africa [2]. These were typically occurs in Sub-Saharan Africa on limited area with number of cases from tenth to hundreds and number of victims not exceeding three hundred. West Africa Ebola outbreak 2014 (WAEO)

is currently the largest one in human history [6, 7]. There are several differences between WAEO 2014 and previously occurred outbreaks.

The differences are in size of geographically spread, number of cases and duration. Previously occurred outbreaks are mostly limited on villages closely related with rainforests and do not widespread to the large area, but WAEO exceeded not only countries borders (four countries of Equatorial Africa: Guinea, Liberia, Sierra Leone and Nigeria), but also the continent borders (Spain and America) [6]. Number of laboratory confirmed human cases were lower (maximum 425, Sudan 2000-2001) and duration of previously described outbreaks were shorter than one year. WAEO 2014 crossed also these established rules. The number of reported cases is almost 20,000, and it is assumed that outbreak takes more than one year, because number of cases and deaths still increase.

2. Virology

EBOV belongs to the genus Ebolavirus and family Filoviridae, in the Mononegavirales [8]. EBOVs are linear, single-stranded RNA viruses which genome has approximately 19 kb with a coding capacity for seven structural proteins [9]. The noncoding sequences located at the 3' and 5' ends of the viral genomes are of significantly different lengths [10, 11]. The ribonucleoprotein complex of virion consists of the genomic RNA encapsulated by the nucleoprotein, which is associated with VP30, VP35, and RNA-dependent RNA polymerase to the functional transcriptase-replicase complex [12]. VP35 serves also in an interferon antagonism [13] and protein VP40 is plugged as the matrix protein and also mediates formation of virions [14]. Structural protein (VP24) is associated with the virus membrane, interferes with interferon signalling [9]. The glycoprotein is the only transmembrane surface protein of the virus and forms trimeric spikes consisting of glycoprotein 1 and 2 [10]. The virion is pleomorphic, producing 'U'- shaped or '6'-shaped structure, but the predominant forms of the virion most frequently seen by electron microscope are long and filamentous, which gave the Filovirus family its name [1, 8, 9]. The ZEBOV is responsible for the current outbreak, which have been introduced in West Africa from Central Africa in the last few decades [15]. Ebola virus, infections with the ZEBOV have the highest case-fatality rates (60–90%) followed by those for the SUDV (40–60%). Case fatality of BDBV was estimated to 25%, based on one outbreak. Only one patient with Tai Forest Ebola virus was identified and survived [16].

The incubation period of Ebola is usually 1 - 2 weeks. Initial clinical symptoms are nonspecific (fever alternating chills, myalgia, and nausea). This stage is followed by influenza-like symptoms (rhinitis, cough, and breath difficulties and body aches); gastrointestinal symptoms (diarrhea, nausea, vomiting), and finally haemorrhagic symptoms, multi organ failure and deaths, which are connected with severe cases [1, 2].

Diagnosis of Ebola can be difficult initially, because the symptoms can be confused with those of diseases that are more common in Equatorial Africa such as malaria or Lassa fever [2]. Infection occurs through close contact with body fluids (skin or mucosal surfaces of infected patients). Most of cases occur at persons, who care about patients (family members or medical personal). Amplified transmission occurs in hospitals or health care centres, approximately one quarter of cases occurring among health care workers [2].

3. Epidemiology of Ebola viruses

The first outbreak of Ebola in Sudan (SUDV, 284 cases, mortality rate of 53%), occurred in Nzara, Maridi and the surrounding area and was spread mainly through close personal contact within hospitals and many medical care personnel were infected [17]. The second Ebola virus emerged from Yambuku, Zaire (ZEBOV, 318 cases, mortality 88%), occurred in Yambuku, and was spread by close personal contact and by use of contaminated needles [18]. The third strain of Ebola, RESTV was identified in 1989 when infected monkeys were imported into Reston (USA) from the Philippines. Only few people were infected with RESTV (seroconverted), but Ebola haemorrhagic fever never

developed in them. The last known strain of Ebola, TAFV was discovered in 1994 when a female ethologist performing a necropsy on a dead chimpanzee from the Tai Forest, Cote d'Ivoire, accidentally infected herself during the necropsy.

According to Feldman et al. Ebola haemorrhagic fever is thought to be a classic zoonosis [1]. Fruit bats are believed to be the natural reservoir [19]. On the other hand Gire et al. sustained human-to-human transmission during 2014 WAEO, with no evidence of additional zoonotic sources [7]. By Hayden et al. the high lethality of filovirus infection in monkeys, humans and other apes suggested that primates were not the natural hosts: if a virus kills too many of its hosts, then it cannot propagate and dies out [3]. It is obvious that despite the tremendous effort of researchers, Ebola's natural reservoir was never identified.

4. 2014 WAEO and previous Ebola epidemics

EVD was firstly identified in 1976 [5] during two outbreaks, which were observed concurrently in Southern Sudan, and in Northern Zaire [16, 20]. One year later was noticed one fatal case of Ebola in Zaire [21], and even later small outbreak in 1979 [22]. Based on serological tests, strains from Zaire and Sudan were different, and studies in mice and monkeys also confirmed differences in pathogenicity [23]. After epidemics in period 1976 - 1979 there is no evidence of EVD outbreaks between 1979 and 1994. But after 1994 the number of outbreaks increased, even that two new Ebola virus species were discovered, namely TAFV in 1994 in the Ivory Coast and BDBV in 2007 in Uganda [8].

Ebola haemorrhagic fever remains a plague for the population of equatorial Africa, with an increase in the numbers of outbreaks and cases since 2000 [1]. The current outbreak is thought to have begun in southeastern Guinea in December 2013, when a two-year-old boy died of a mysterious illness that quickly spread to family members and health-care workers [3, 15]. However, onset of the new outbreak was not recognized until March 2014 [15], which facilitated the spread to Sierra Leone, Liberia and Nigeria [24]. The June 18, 2014 the total EVD case count reported for all three countries was 528, including 364 laboratory-confirmed, 99 probable, and 65 suspected cases, with 337 deaths (case-fatality rate = 64%). Most of cases were reported in Guinea (398 cases), Sierra Leone (97 cases) and Liberia (33 cases) [25]. The August 8, 2014 the World Health Organization (WHO) declared the Ebola virus disease (EVD) outbreak in West Africa as a Public Health Emergency of International Concern (PHEIC) [25, 26] and highlighted the need for international cooperation to control the outbreak. The August 29, 2014 WHO noticed 3052 cases and 1546 deaths [25]. By September 18, 2014 the WHO reported of 5335 cases (confirmed, suspected and probable) with 2622 deaths, resulting in a case fatality rate of around 50% [27]. On the September 18, 2014 a total of 5335 cases with 2622 reported deaths have been notified, in Guinea, Liberia, and Sierra Leone [25]. According to WHO, the October 31, 2014, 13 540 people have been diagnosed with Ebola virus disease in eight countries, including 4951 deaths [25]. Dedicated doctors, nurses, and other health-care workers have made great efforts to contain the epidemic. WHO reports that 450 of these health-care workers have developed the disease and more than 230 died [25]. As of December 18, 2014 this outbreak has 19078 reported cases resulting in 7413 deaths [20, 28]. One month later, 7th January, number of cases was 20747 and 8235 deaths [25].

5. Transmission

It is often mentioned that Ebola virus is introduced into human populations by handling of infected animal (bush meat and carcasses) [1, 8, 19]. If the first source of transmission is an animal found dead or hunted in the forest, followed by person-to-person transmission from index case to family members or medical-care staff [8, 17, 18]. Animal-to-human transmission occurs when people come into contact with tissues or body fluids of infected animals, especially nonhuman primates [30]. Animal-to-human transmission has been reported in Côte d'Ivoire, an etiologist was infected through handling an infected, dead chimpanzee [16].

Year	Country, village	EboV subtype	Number of human cases	Number of deaths	Mortality	source and spread of infection
1976	Zaire, Yambuku	Ebola virus	318	280	88%	contaminated needles and syringes in hospitals - spread by close contact
1976	Sudan, Nzara and Maridi	Sudan virus	284	151	53%	spread by close contact within hospitals, many hospital staff were infected
1976	England	Sudan virus	1	0		Laboratory infection, accident - stick of contaminated needle
1977	Zaire, Tandala	Ebola virus	1	1	100%	Noted retrospectively
1979	Sudan, Nzara and Maridi	Sudan virus	34	22	65%	Recurrent outbreak at the same site as the 1976
1989	USA, Viriginia and Pennsylvania	Reston virus	0	0		EboV was introduced into quarantine facilities by monkeys from the Philippines
1990	USA, Viriginia	Reston virus	4	0		Reintroducuing into quarantine facilities by monkeys from the Philippines
1989-1990	Philippines	Reston virus	3	0		Source: macaques from USA. Three workers (animal facility) developed antibodies, did not get sick.
1992	Italy	Reston virus	0	0		Source: monkeys imported from the Philippines, that was also involved in the United States episodes.
1994	Gabon	Ebola virus	52	31	60%	Initially thought to be yellow fever, identified as Ebola in 1995
1994	Côte d'Ivoire	Taï Forest virus	1	0		Scientist became ill after autopsy on a wild chimpanzee (Tai Forest).
1995	Democratic Republic of Congo (Zaire)	Ebola virus	315	250	81%	Case-patient worked in the forest, spread through families and hospitals.
1996	Gabon	Ebola virus	37	21	57%	Source: chimpanzee found dead in the forest was eaten by hunters, spread in family members
1996-1997	Gabon	Ebola virus	60	45	74%	Case-patient was a hunter from forest camp. Disease was spread by close contact.
1996	South Africa	Ebola virus	2	1	50%	Infected medical professional traveled from Gabon to Johannesburg, nurse who took care became ill and died.
1996	USA, Texas	Reston virus	0	0		Source: monkeys imported from the Philippines.
1996	Philippines	Reston virus	0	0		Source: monkey in export facility in the Philippines
1996	Russia	Ebola virus	1	1	100%	Laboratory contamination
2000-2001	Uganda	Sudan virus	425	224	53%	Providing medical care to Ebola case-patients without using adequate personal protective measures
2001-2002	Gabon	Ebola virus	65	53	82%	Outbreak occurred over the border of Gabon and the Republic of the Congo.
2001-2002	Republic of the Congo	Ebola virus	57	43	75%	Outbreak occurred over the border of Gabon and the Rep. of the Congo.
2002-2003	Republic of the Congo	Ebola virus	143	128	89%	Outbreak in the districts of Mbomo and Kéllé in Cuvette Ouest Département.
2003	Republic of the Congo	Ebola virus	35	29	83%	Outbreak in villages located in Mbomo distric, Cuvette Ouest Départemen.
2004	Sudan, Yambio	Sudan virus	17	7	41%	Outbreak concurrent with an outbreak of measles, and several cases were later reclassified as measles.
2004	Russia	Ebola virus	1	1	100%	Laboratory infection.
2007	Democratic republic of the Congo	Ebola virus	264	187	71%	The outbreak was declared over November 20. Last death on October 10.
2007-2008	Uganda	Bundibugyo virus	149	37	25%	First reported occurrence of a new strain
2008	Philippines	Reston virus	6	0		Six workers (pig farm) developed antibodies, did not become ill.
2008-2009	Democratic republic of the Congo	Ebola virus	32	15	47%	
2011	Uganda	Sudan virus	1	1	100%	The Uganda Ministry of Health informed the public a patient with suspected Ebola Hemorrhagic fever died on May 6, 2011 in the Luwero district, Uganda.
2012	Uganda, Kibaale	Sudan virus	11	4	36%	Laboratory tests of blood samples were conducted by the UVRI and the CDC.
2012	Democratic republic of the Congo	Bundibugyo virus	36	13	36%	This outbreak had no link to the contemporaneous Ebola outbreak in the Kibaale, Uganda.
2012-2013	Uganda	Sudan virus	6	3	50	CDC assisted the Ministry of Health in the epidemiology and diagnosis of the outbreak.
2014	Democratic republic of the Congo	Zaire virus	66	49	74%	The outbreak was unrelated to the outbreak of Ebola in West Africa.

Table 1: Ebola outbreaks between 1976 and 2014, adapted from WHO [29]

It was laboratory confirmed that the deaths of chimpanzees were indeed by the Ebola virus. In Gabon and the Republic of the Congo, outbreaks in humans were associated with extensive deaths of chimpanzees and gorillas [31]. After analysis of the risk factors for transmission of EBOV from anthropological point of view, it is noticeable that the increase in Ebola outbreak since 1994 is frequently associated with drastic changes in forest ecosystems in tropical Africa [8]. Transmission of Ebola could be connected with human activities like hunting, farming, ministration of funeral rites, processing of bush meat from bats and exceptionally because of scientific activities [8, 32]. Sexual transmission has been suggested in humans since filoviruses can be found in semen [33]. Aerosol infection is questioned since people sharing the same space with infected persons do not contract the infection. Even though aerosol infection of nonhuman primates (NHP) has been demonstrated in the laboratory [34]. The highest risks of transmission of WAEO are people visiting and taking care of infected patients in their homes or in hospitals.

6. Therapy and prevention

Specific treatment or vaccine against the EBOV is not commercially available. Treatment strategies of EVD are pointed on the early start of supportive care which provably improved the survival of infected patients. They include rehydration therapy or giving intravenous fluids as well as treating symptoms.

WHO approved the use of convalescent serum and whole blood products to treat affected patients [35].

Regarding passive immunotherapy, the most promising drug seems to be ZMapp that combines three humanized monoclonal antibodies [36]. Specific antiviral EVD treatment strategies are still in the experimental phase [27]. There are three most discussing experimental antiviral drugs (TKM-Ebola, Favipiravir and BCX4430). TKM-Ebola interfere RNA molecule to silence expression of two Ebola genes which virus needs to replication. This drug prevented infection in all the laboratory animals given a lethal dose of Ebola virus [37]. Favipiravir (T-705), a viral RNA polymerase inhibitor, has shown efficiency against EV in mice [38]. BCX4430 (nucleoside analog that blocks viral RNA synthesis) has shown promising results in rodents and monkeys, but pre-clinical toxicology and phase 1 data for this drug are lacking [39]. The prevention of EVD requires improving our understanding of the epidemiology of the disease, especially the role of wildlife, including bats, in the transmission of Ebola virus to humans [8].

7. Conclusions

West Africa Ebola outbreak 2014 is occurring on a scale not seen before in Equatorial Africa. Such events perform as reminders of the potential of viruses to cause pandemic and endanger the health of the world's population. Rapid and wide spread is facilitated by insufficient medical facilities, poor sanitation of medical material, travel, air plane transport and unsafe burial practices. Because of the initial nonspecific symptoms of EVD (fever, nausea and flu-like symptoms) is difficult to distinguish EVD from other Africa endemic diseases and set up preventive and treatment strategy. Specific antiviral drug against EVD are still in the experimental phase. And there is no available and effective vaccine. It is available only supportive treatment strategies, due to this facts medical stuff have nearly empty hands. There is need to understand transmission on example of the current Ebola virus outbreak and development of animal model for testing of novel vaccines and antiviral drugs.

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Conflicts of Interest

The authors declare they have no potential conflicts of interests concerning drugs, products, services or another research outputs in this study. The Editorial Board declares that the manuscript met the ICMJE „uniform requirements" for biomedical papers.

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