# The Pathogenesis and Countermeasure of Ebola Virus Disease

Kedu Jin[1, 2, *]

[1]School of China Pharmaceutical University, China

[2]School of Strathclyde University, The UK

*2590481254@qq.com

**Abstract.** Ebola virus disease(EVD), previously known as Ebola hemorrhagic fever, is a serious and frequently fatal illness caused by Ebola virus (EBOV).Between 2014 and 2016, the West Africa region faced the most substantial Ebola epidemic to date, which devastated Guinea, Sierra Leone, and Liberia, resulting in infections exceeding 28,000 and fatalities surpassing 11,000. Subsequently, from 2017 to 2020, various provinces in the Democratic Republic of Congo's western and eastern regions encountered Ebola outbreaks, leading to over 2,300 fatalities. The most recent instance concluded in the Équateur Province on November 19, 2020. EBOV posed an immense challenge to international public health; however, it also yielded valuable insights into the pathogenesis, natural history, clinical manifestations, treatment, prevention, and control strategies of Ebola. Especially, The emergence of the epidemic generated an abundance of authentic and dependable research data and case studies, which facilitated extensive testing of certain clinical trial drugs, thereby establishing a robust foundation for future therapies of EVD. In the present review, we aim to delineate the pathogenesis of EBOV and compile a summary of the most recent countermeasures.

**Keywords:** EVD; EBOV; pathogenesis; countermeasure.

## 1. High Infectivity:

The Ebola virus was initially identified in the Democratic Republic of Congo in 1976, primarily via contact with wildlife, and it is capable of being transmitted from individual to individual. The basic reproduction number R0 of the EBOV (in epidemiology, the average number of people that an infected person with a contagious disease will infect in the absence of outside intervention and assuming that no one has immunity) is 2, which means that on average, each patient in an outbreak will infect two other people; those two people either die from the disease or recover from it. This may be alarming, but it's worth noting that there are many other infectious diseases with higher R0 values. For example, the R0 value of SARS is 4, and the R0 value of measles is 18, as shown in Fig.1. In fact, a fundamental disparity between Ebola and the majority of other lethal contagious diseases is that the virus does not propagate proactively among carriers until the afflicted individual exhibits symptoms. Consequently, despite the R0 value of 2 (for Ebola) being comparatively low among numerous alarming infectious diseases, this metric still implies that the infected demographic may disseminate the virus at a rate of approximately doubling every 1-2 week interval; the prevailing circumstances in third-world countries grappling with an Ebola epidemic amply exemplify this issue.

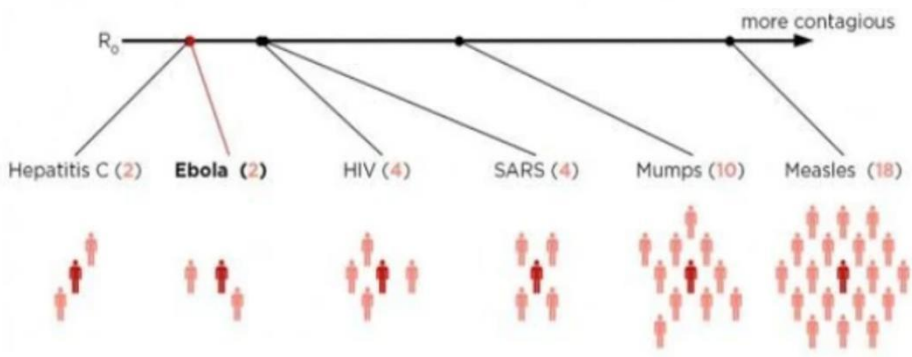


**Fig.1** The basic reproductive numbers (R0 values) of Ebola and several common infectious diseases (Hepatitis C, HIV, SARS, Mumps, Measles)

## 2. High mortality:

Ebola virus is predominantly categorized into six distinct species, encompassing the Zaire Ebola virus, Sudan Ebola virus, Taï Forest Ebola virus, Bundibugyo Ebola virus, Lloviu Ebola virus, and Bamboo Ebola virus. Among these, the Zaire Ebola virus exhibits the highest fatality rate, reaching 88%. This virus has been responsible for the pandemics that devastated Africa in 1976, 2014, and 2018, resulting in the loss of tens of thousands of lives and earning it the moniker "the scythe of death." The EVD outbreaks statistics is shown in Table1.

**Table1.** Ebola virus disease outbreaks statistics[1]

| Country(year) | Case-fatality rate(%) | Number of cases |
|---|---|---|
| COD(then Zaire)(1976) | 88.1 | 318 |
| COD(then Zaire)(1977) | 100.0 | 1 |
| Gabon(1994-1995) | 61.5 | 52 |
| COD(then Zaire)(1995) | 77.3 | 317 |
| Russiaa(1996) | 100.0 | 1 |
| Gabon(1996) | 67.7 | 31 |
| Gabon, also exported to South Africa(1996-1997) | 74.2 | 62 |
| Gabon,COG(2001-2002) | 78.2 | 124 |
| COG, also exported to Gabon(2002) | 90.9 | 11 |
| COG(2002-2003) | 89.5 | 143 |
| COG(2003-2004) | 82.9 | 35 |
| Russiaa(2004) | 100.0 | 1 |
| COG(2005) | 81.8 | 11 |
| COD(2007) | 70.5 | 264 |
| COD(2008-2009) | 46.9 | 32 |
| Guinea, also exportedto Liberia,Mali, Senegal, Sierra Leone and USA;from Liberia,cases were exported to France, Germany, Netherlands, Nigeria, Norway, Spain and USA and, from Sierra Leone, to ltaly,UK, Switzerland and USA(2013-2016) | 39.5 | 28,652 |
| COD(2014) | 71.0 | 69 |
| COD (2017) | 50.0 | 8 |
| COD(2018) | 61.1 | 54 |
| COD,also exported to Uganda(2018 to present) | 66.3 | 3,324 |

Country abbreviations are as used by the International Organization for Standardization (ISO). COD, Democratic Republic of the Congo; COG, Republic of the Congo. a Laboratory-acquired infection. Cited from Jacob S T..

## 3. Current diagnosis methods of EVD：

Clinically, differentiating the Ebola virus disease from other infectious diseases, such as malaria, typhoid fever, and meningitis, can be challenging. A multitude of symptoms exhibited by the Ebola virus disease bear resemblance to those associated with pregnancy. Considering the potential risks to both pregnancy and the mother's health, it is advisable for pregnant women to undergo testing for the Ebola virus disease promptly upon suspicion of infection.The following diagnostic methodologies can be employed to ascertain whether the symptoms are attributable to Ebola virus infection: enzyme-linked immunosorbent assay, antigen detection, serum neutralization testing, reverse transcription

polymerase chain reaction (RT-PCR) analysis, electron microscopy, and viral isolation via cell culture techniques.

## 4. Aim

Ebola virus disease (EVD) is highly contagious and lethal. Drawing upon the enhancement of certain contemporary diagnostic modalities and the extant research literature on the Ebola virus, the objective of this investigation is to delve into the pathogenesis and instituted countermeasures of EVD through an integrative and comparative approach of substantial depth.

## 5. Discussion

The Ebola virus (EBOV) is a member of the Filoviridae family, and it is a negative-sense RNA virus[2]. The EBOV genome has seven genes, namely, nucleoprotein (NP), viral polymerase complex protein 35 (VP35), matrix protein (VP40), glycoprotein (GP), minor nucleoprotein (VP30), membrane-associated protein (VP24) and polymerase (L-protein) as shown in Figure 2[3].

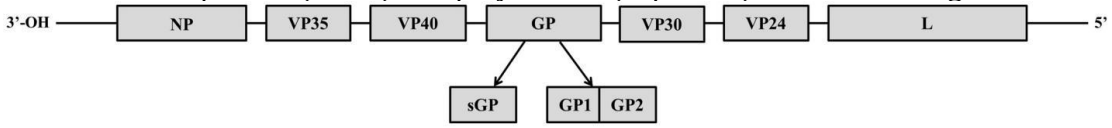


**Fig.2** EBOV genome—NP, VP35, VP40, GP, VP30, VP24 and L in order from the 3′ to 5′ end. GP encodes two proteins—secreted GP (sGP), which is a dimer, and transmembrane protein, which a trimer of three disulfide-linked GP1-GP2 heterodimers[3].

The Ebola virus life cycle involves initial infection through contact with infected bodily fluids, followed by an incubation period of 2-21 days. During this time, the virus replicates within host cells, particularly immune cells, before causing symptoms such as fever and muscle pain. As the infection progresses, the virus is shed in bodily fluids, making the individual contagious. In severe cases, this can lead to organ failure and death. The virus can continue to spread through direct contact with infected individuals or their fluids, emphasizing the importance of infection control measures to prevent transmission. The details are shown in Figure 3.

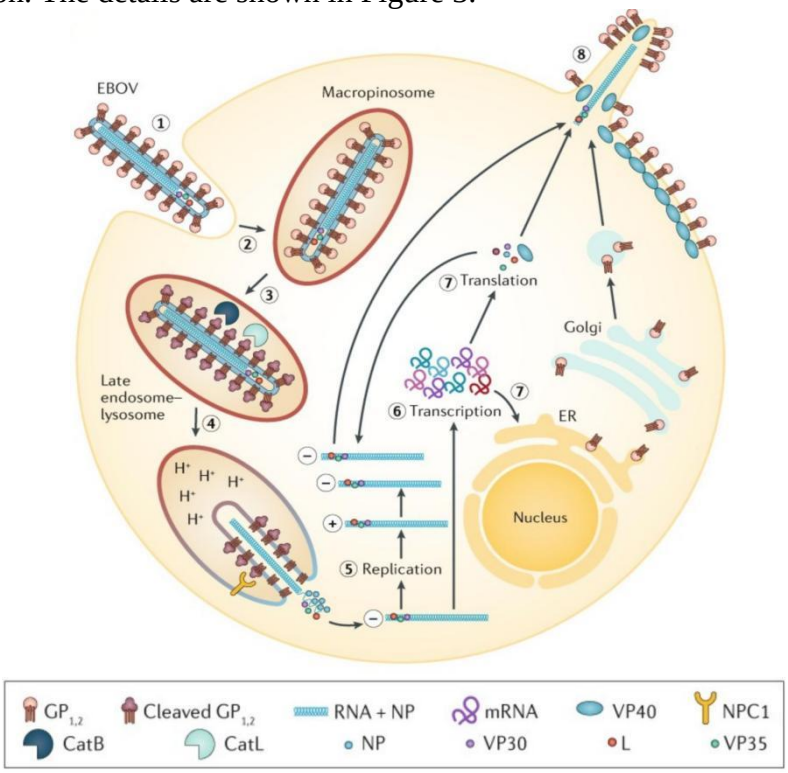


**Fig.3[1]** The life cycle of EBOV

Symptoms of EVD in humans normally occur after an incubation period of 2–21 days (19–21). There are typically three phases of illness; it starts with a few days of nonspecific fever, headache, and myalgia, followed by a gastrointestinal phase in which diarrhea and vomiting, abdominal discomfort, and dehydration are prominent as shown in Figure 4.

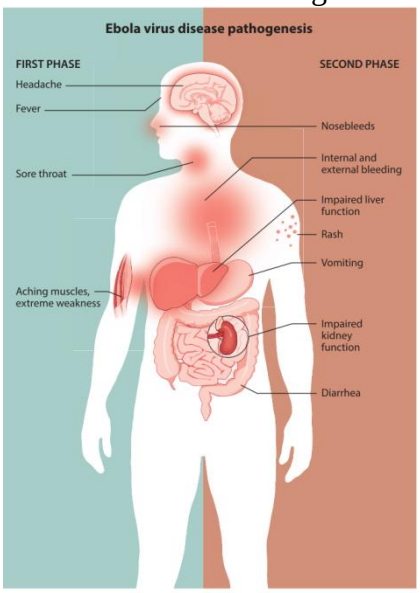


**Fig.4 [4]** Ebola virus disease pathogenesis

Ebola virus particles infiltrate the host's system through either microscopic or macroscopic breaches in the skin, or through direct transmission via mucosal linings. The primary cellular targets of the infection encompass macrophages and dendritic cells. These infected cells migrate to the regional lymph nodes, replicating the virus progeny in the process. Subsequently, through the suppression of the intrinsic, innate, and adaptive immune responses, the progeny virions are distributed systemically, leading to infections in secondary target cells across nearly every organ within the body.Significant organ-specific interactions transpire within the gastrointestinal tract, liver, and spleen, manifesting through specific markers of organ injury or dysfunction that correlate with human disease outcomes. Speculative manifestations are denoted by question marks. RIG-I refers to the retinoic acid inducible gene I, a receptor in the antiviral innate immune response. The details are shown in Figure 5.

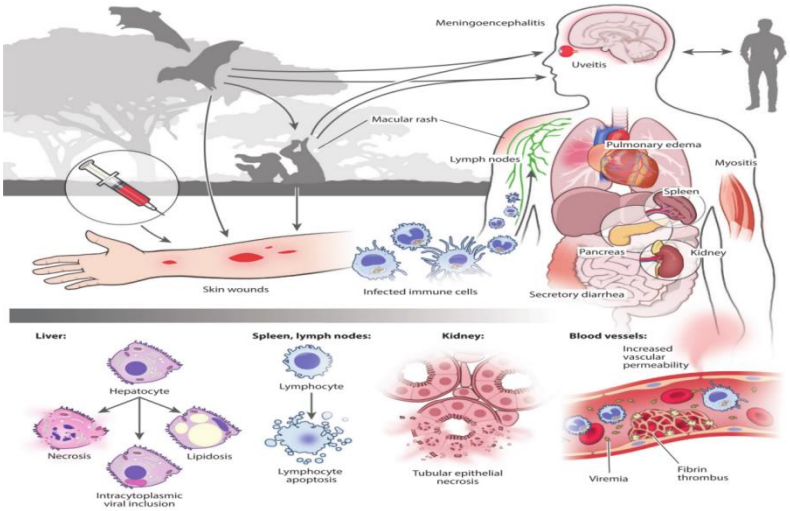


**Fig.5[5]** The transmission and pathogenesis of ebolavirus infection.

The conceptualized clinical course of acute Ebola Virus Disease (EVD) typically evolves through several stages over time. It begins with an incubation period of 2 to 21 days, followed by a sudden onset of flu-like symptoms including fever, headache, and muscle pain. As the disease progresses,

patients may experience severe vomiting, diarrhea, and abdominal pain, leading to dehydration and electrolyte imbalances. The hallmark of EVD is its hemorrhagic manifestations, which can range from minor bruising to severe internal and external bleeding. In the most critical phase, patients may develop multi-organ dysfunction syndrome, with complications such as acute respiratory distress syndrome, kidney failure, and liver damage. The progression and severity of EVD can be influenced by various factors, and early detection, isolation, and supportive care are vital for patient survival. The details are shown in Figure 6.

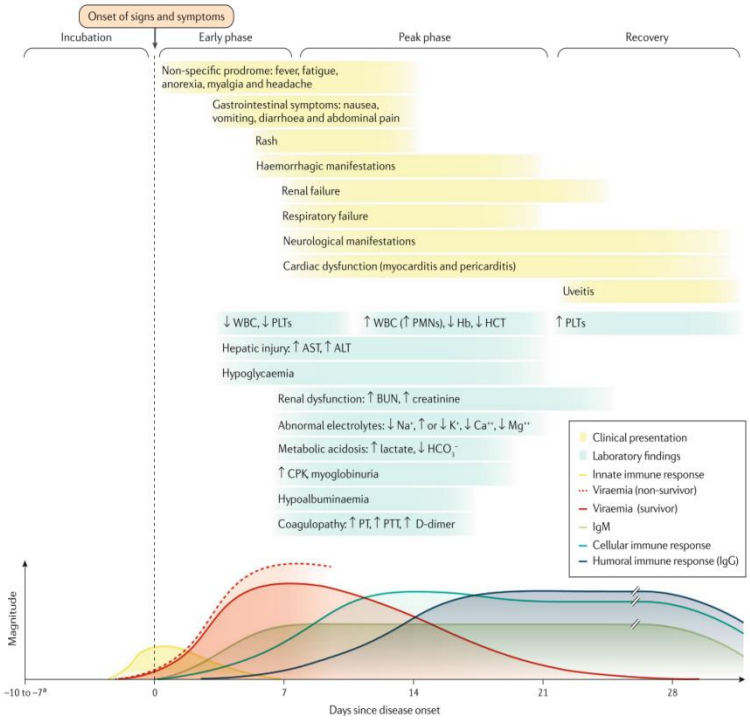


**Fig6[1]** Conceptualized clinical course of acute EVD over time

Vaccines are instrumental in preventing the spread of the Ebola virus, providing a critical shield against a disease with high fatality rates. They not only save lives by offering immunity but also contribute to global health security by preventing outbreaks that can devastate communities and economies. The development and use of Ebola vaccines exemplify the power of medical science in combating infectious diseases and underscore the importance of continued research and innovation in vaccine technology.

The rVSV-ZEBOV/Ervebo vaccine has been granted the European Commission a conditional marketing authorization, and WHO pre-qualification. It has now been approved for medical use in the European Union and in the United States. The Zabdeno vaccine has been granted approval by Committee for Medial Products for Human Use -European Medicines Agency (CHMP-EMA) for active immunization of individuals aged 18 years and older at risk of infection with the Ebola virus. Additional information about other candidate vaccines is provided in Table 2.[6]

**Table 2.** Status of candidate vaccines

| Company/institution/ country | (Vaccine name)/Ebola component glycoprotein | Vector | Administration | Storage temperature | Target population | Comments |
|---|---|---|---|---|---|---|
| Merck USA/Public Health Agency Canada | (Ervebo)Recombinant VSV-ZEBOV-Ebola Kikwit strain Replication competent vaccine | VSV | Single dose | 60°C to −80°C for 36 months and 2°C–8°C for 14 says | Active immunization (reactive use) of at risk subjects ≥18 years of age | 2016- granted Breakthrough Therapy Designation by the US FDA and PRIME status by the European Medicines Agency (EMA) and in 2019, granted medical use in EU and USA. Used extensively in the Kivu Ebola epidemic under a compassionate use protocol |
| Johnson & Johnson (USA) and MVA-BN Filo, Bavarian Nordic (Denmark) | (Zabdeno)MVA-BN-Filo encodes Ebola virus, Sudan virus, and Marburg virus glycoproteins, and Tai Forest virus nucleoprotein | Human adenoviral serotype 26 or MVA | Heterologous prime boost regimen | Ad26.ZEBOV: 20°C or 60°C for up to 60 months and +2 to +8°C for up to 12 months<br>MVA-BN-Filo: 20°C or 60°C for up to 60 months and +2 to +8°C for up to 6 months | Adults and children ≥ 1 year of age | Granted approval by Committee for Medial Products for Human Use -European Medicines Agency (CHMP-EMA) in 2020 as a two-dose regimen for the prevention of Ebola virus disease. Seeking licensure under the Animal Rule and/or to European Medicines Agency. Collaborative. |
| GlaxoSmithKline (UK) and, for MVA-BN-Filo, Bavarian Nordic (Denmark)- NIAID/GSK | (ChAd3-EBO-Z) with or without MVA-BN-Filo Ebola virus, Mayinga strain (1976) | Chimpanzee adenoviral serotype 3 or MVA | Single dose or heterologous prime-boost regimen | | | **Ongoing clinical evaluation!** |
| Academy of Military Medical Sciences and CanSino Biologics (China) | (Ad5-ZEBOV) Ebola virus, Makona strain (2014) | Human Adenoviral serotype 5 | Single dose or homologous prime-boost regimen | Freeze-dried powder, stable for more than 2 weeks even if kept at a temperature of 37°C; | | Licensed in China |
| Gamalei Scientific Research Institute of Epidemiology and Microbiology (Russia) | (GamEvac-Combi and GamEvac-Lyo) Monovalent Zaire (Makona) | VSV and Ad5-vectored vaccine | Heterologous prime boost regimen | 16°C to −20°C for 12 months 4°C for lyophilized formulation | 18–55 years | Licensed in Russia |
| Novavax, USA | (NVX-CoV2373). Nanoparticle recombinant Ebola GP Vaccine) Monovalent Zaire (Makona) | Contains the full-length SARS-CoV-2 spike protein and Novavax' patented Matrix-M1 adjuvant | 2 doses 21 days apart, | 2° to 8°C for six months, and 24 hours at room temperature | 18–65 years | Efficacy 89.3 %. |
| Inovio Pharmaceuticals, USA | (INO-4201 DNA vaccine) Plasmid of Ebola outbreak strains from 1976–2006 | | 2 doses four weeks apart | +2°C to +8°C for 3 years and 25°C for 1 year 37°C for 1 month 60°C for several days | ≥ 18 years | In 95% (170/179) of evaluable subjects generated an Ebola-specific antibody immune response, |
| FBRI SRC VB VECTOR, Rospotrebnadzor, Russia | (EpivacEbola) Monovalent Zaire (Makona) | | 2 doses (prime + boost on 28 days) | 2–8°C for 1 year Can extend shelf life to 2 years | 18–55 years | Licensed in Russia since 2016 |

VSV-vesicular stomatitis Indiana virus. MVA = modified vaccinia Ankara virus. Ad5=human adenoviral serotype 5. *The year the strain (from which the glycoprotein was derived) was isolated is given in brackets.

Early case diagnosis and isolation of patients with EVD during outbreaks is important.516 A surveillance system is essential in guiding the control measures required to reduce morbidity and mortality caused by EVD.[8] Control strategies during an Ebola outbreak include proactive case detection, contact tracing and management, safe and dignified burials, and prevention of new infections. Successful contact tracing requires skills in the assessment of EVD symptoms, interviewing techniques.[9]

## 6. Conclusion

The Ebola Virus Disease (EVD) has posed a significant threat to global health, with its high fatality rates and rapid transmission. The pathogenesis of EVD, involving initial infection, incubation, and systemic spread leading to severe organ dysfunction, underscores the need for robust diagnostic and therapeutic strategies. The development of vaccines such as rVSV-ZEBOV/Ervebo and the Zabdeno vaccine represents a significant stride in combating EVD. These vaccines, along with improved diagnostic tools and public health interventions, offer a ray of hope in controlling and preventing future outbreaks.

In conclusion, the collective efforts in research, vaccine development, and public health strategies have been pivotal in managing EVD. The ongoing commitment to scientific innovation and global health preparedness is crucial for mitigating the impact of EVD and safeguarding against potential future pandemics. As we continue to learn from past experiences, the global health community must remain vigilant and proactive in the face of emerging infectious diseases.

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