

Vaccine Development and Immunological Aspects of Ebola Virus Disease (EVD): An Update

Tauseef Ahmad^{1,2}, Haroon^{3**}, Muhammad Khan^{4#}, Fazal Mehmood Khan^{5#}, Taha Hussein Musa^{1,2#}, Alfonso J Rodriguez-Morales^{6,7} and Jin Hui^{1,2}



¹Department of Epidemiology and Health Statistics, School of Public Health, Southeast University, Nanjing 210009, China

²Key Laboratory of Environmental Medicine Engineering, Ministry of Education, School of Public Health, Southeast University, Nanjing, China

³College of Life Science, Northwest University, Xian, China

⁴Department of Genetics, Centre for Human Genetics, Hazara University Mansehra, Khyber Pakhtunkhwa, Islamic Republic of Pakistan

⁵Key Laboratory of Special Pathogens and Biosafety, Centre for Emerging Infectious Diseases, Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan China

⁶Public Health and Infection Research Group, Faculty of Health Sciences, Technological University of Pereira, Pereira, Colombia

⁷Biomedicine Research Group, Faculty of Medicine, Autonomous University Foundation of the Americas, Pereira, Risaralda, Colombia

#These authors contributed equally to this work

*Corresponding author: Haroon, College of Life Science, Northwest University, Xian, China

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ABSTRACT

Infectious diseases emergence and re-emergence over the last 50 years have increased. Ebola virus disease (EVD) has been a public health emergency of international concern, given its high risk of transmission, and its high case-fatality rate can reach over 40%. The EVD first emerged in 1976. Epidemics, particularly since 2014, have called for interventions, mainly those preventive and the specific aim of developing an effective vaccine. There are currently no licensed vaccines available to prevent EVD infections. However, since the discovery of EVD, different vaccine strategies, including monovalent, bivalent, and multivalent candidates, have been studied. In such a critical time, the health care community played an active role by fast-tracking an EVD vaccine, which was not available to stop the outbreak. The outbreak intensity could be reduced much more if VSV-ZEBOV had been assessed for safety after the initial stages of the pre-clinical study.

Abbreviations: DRC: Democratic Republic of Congo, EVD: Ebola Virus Disease, EVC: Ebola Vaccine Candidates, RABV: Rabies Virus, VLP: Ebola Virus-Like Particles, CMV: Cytomegalovirus, VSV: Vesicular Stomatitis Virus, VEEV: Venezuelan Equine Encephalitis Virus

Background

Ebola Virus Disease (EVD) has been a public health emergency of international concern, given its high risk of transmission, and its high case-fatality rate can reach over 40%. Epidemics, particularly since 2014, have called for the need for interventions, mainly those preventive and the specific aim of developing an effective vaccine [1].

Ebola Virus Disease Vaccine

Infectious diseases emergence and re-emergence over the last 50 years have increased [1] and challenging public health at local, regional, national, and international levels. EVD first seems in 1976 [2], and till now, putting millions of lives at risk and killed across the world, including Africa. The current ongoing EVD outbreak in

the Democratic Republic of Congo (DRC) accelerated the strategies and efforts to test vaccine candidates [3]. All these efforts aim to ensure public health safety and control further spreading and illnesses due to EVD. In the past, the vaccine development EVD has been hampered by lower priority in the public health sector, the need for high-level biocontainment, and a general lack of interest among pharmaceutical companies [1]. In West Africa, the response to highly pathogenic infectious diseases and rare emerging diseases has demonstrated that public health measures interfere with religion, politics, tradition, and human behavior [4].

Ebola Vaccine Development

There are currently no licensed vaccines available to prevent EVD infections [5]. However, since the discovery of EVD, different vaccine strategies, including monovalent, bivalent, and multivalent candidates, have been studied [6]. The thirteen Ebola Vaccine Candidates (EVC) are currently in different trial phases [5]; it may be adenovirus (Ad), cytomegalovirus (CMV), Ebola virus lacking the gene for VP30 (EBOVVP30), human parainfluenza virus type 3 (HPIV3); modified vaccinia virus Ankara (MVA); Rabies Virus (RABV), Venezuelan Equine Encephalitis Virus (VEEV), Ebola Virus-Like Particles (VLP), and Vesicular Stomatitis Virus (VSV), with different trail vectors [1,7]. Although the purpose of the vaccine trials is to evaluate vaccine safety and immunogenicity in human trials, while in phase I, there are eight vaccines, two vaccines are in the phase II stage, and phase III had one vaccine [8]. Evaluation of the vaccine's efficacy during pre-clinical and clinical studies must be carried out with the vaccine's approval. Additionally, outside of the epidemic period, clinical protection against EVD in human populations is impossible to observe. As a result, EVD vaccines are currently evaluated using the primary endpoint of immunogenicity.

There is no definite evidence that antibody response is the human efficacy association of defense or surrogate endpoint, an immune response to vaccine correlated with vaccine-induced safety, and may vary depending on the vaccine platforms [7,9]. Previous studies focused on introducing a fast-acting immunization regimen with a protective response. However, after the supposition of the outbreak, the efficacy of vaccine-induced safety and potential benefits needs to be given more consideration of futures challenges [10]. Therefore, safety and immunogenicity accumulate under active clinical development for all candidate vaccines, measured after both priming and boosting, display detectable humoral, and cellular immune responses [11]. Though, there is limited follow-up time to document the maintenance of these immune responses. Previous studies focused on introducing a fast-acting immunization regimen with a protective response. However, after the supposition of the outbreak, the efficacy of vaccine-induced safety and potential benefits needs to be given more consideration of futures challenges [10].

Therefore, safety and immunogenicity accumulate under active clinical development for all candidate vaccines, measured after both priming and boosting, display detectable humoral, and cellular immune responses [11]. Though, there is limited follow-up time to document the maintenance of these immune responses. The researchers demonstrated that the immune system reacts to the vaccination, and antibodies induce a wide range of different antibodies against the Ebola virus. Many of the antibodies investigated also exhibit highly neutralizing activity, which is generally essential for the protection against infections [12,5]. Moreover, immune correlates of protection from disease in humans remain unknown, therefore, to facilitate the licensing of drugs and biologics where the efficacy cannot be assessing the effectiveness of the candidate vaccine [8].

The Immune Response to EVD

The initial target of the Ebola Virus is myeloid cells, mainly myeloid dendritic cells, macrophages and monocytes. The specific first targeted cells may differ, depending upon the site of infection. Nevertheless, the most first targeted cells for Ebola Virus infection are macrophages, Stromal Dendritic cells and Langerhans cells [13,14]. These cells are the most favorable sites which give support and help for viral replication. The other cells, like parenchymal cells and endothelial cells, are not the first target of infection. The virus replication in dendritic cells and macrophages disrupts the immune cell antigen presentation and stimulates adaptive immune responses to lead the immune system [14]. The Interferons (IFN) IFN α , IFN β , and (IFN γ) show strong resistance to virus infection and stop directly or indirectly the viral replication by the up-regulation of IFN stimulated genes [15].

Antibody Responses to EVD

The previous studies showed unsatisfactory results of passive immunotherapy against EVD [16-18]. It showed that for protection, cellular immunity has more role compare with humoral immunity. The recent studies showed that specific antibodies for EVD glycoproteins could protect the form of immunotherapy or vaccine-induced antibody-responses, and in human, there is antibody production [19]. In 1995, the antibodies were used to treat the EVD by receiving a blood transfusion from recovering patients [20]. However, it is unclear that whether the patients were in the covering stage or the injected antibodies influence them. The current studies showed that the death of 31% of patients treated with the plasma of recovering patients by comparison with control patients of 38%. So, it showed the limited effect of antibody therapy [21].

Challenges and Future Considerations

When the West African EVD outbreak occurred, the global community was not ready to handle it. There was no vaccine, no

drugs, limited diagnostic facilities, few medical teams, and no plan of action to deal with this outbreak. In such a critical time, the health care community played an active role by fast-tracking an EVD vaccine, which was not available to stop the epidemic. The intensity of the outbreak could be reduced if VSV-ZEBOV was assessed for safety after the initial stages of the pre-clinical study. For the travelers, WHO has not posed and ban to travel an endemic zone for any purpose [22]. Since Ebola outbreaks become usual for DRC, a comprehensive awareness program should be launched to educate the local communities to decrease future attacks. It will be possible to inform the residents about the signs and symptoms of Ebola and the mode of transmission. By emphasizing the importance of getting medical care and immediately reporting suspected individuals. Local authorities should disseminate the health care messages in the local language to aware of the public on a large scale [23].

Author Contributions

All the authors potentially contributed to this manuscript.


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