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REVIEW ARTICLE

Genomics of Ebola Virus: Implications for the 2026 Bundibugyo Outbreak

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ABSTRACT

Ebolavirus disease remains one of the most devastating viral hemorrhagic fevers, causing recurrent outbreaks with high case-fatality rates and substantial socioeconomic disruption. The ongoing outbreak caused by Bundibugyo virus in the Democratic Republic of Congo and Uganda has highlighted important gaps in preparedness because no licensed vaccine or species-specific antiviral therapy currently exists for this Ebolavirus species. Advances in molecular virology have substantially improved understanding of Ebolavirus genome organization, replication, immune evasion, and pathogenesis, thereby informing the development of diagnostics, therapeutics, and vaccine candidates. This review summarizes the genomic organization and replication strategy of Ebolaviruses, with particular emphasis on Bundibugyo virus, and discusses how its genetic divergence from Zaire Ebolavirus complicates vaccine development. The article also examines the biological and public health significance of the ongoing outbreak and identifies future priorities for genomic surveillance and the development of broadly protective medical countermeasures.

KEYWORDS

• Ebola virus • Bundibugyo virus • Genomics • Public health • Viral proteins • Replication • Vaccines • Immune evasion • Pan-ebolavirus • Outbreak

INTRODUCTION

Ebolavirus disease (EVD) is a severe zoonotic infection caused by members of the genus *Orthoebolavirus*, belonging to the *Filoviridae* family. Since the first recognized outbreaks in 1976 in Zaire (now the Democratic Republic

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of Congo or DRC) and Sudan, Ebolaviruses have caused repeated epidemics throughout sub-Saharan Africa, with case-fatality rates ranging from approximately 25% to 90% depending on the virus species, outbreak setting, and availability of supportive care. The unprecedented 2013-2016 West African epidemic transformed global understanding of Ebolavirus biology and accelerated the development of vaccines and therapeutics, particularly against Zaire Ebolavirus, the species responsible for the majority of human infections.[1-3]

Among the six recognized *Orthoebolavirus* species, Bundibugyo virus (BDBV) has received comparatively limited scientific attention because relatively few outbreaks have occurred since its discovery in 2007. This species of Ebolavirus is so called because it was first detected in the Bundibugyo district of western Uganda. Nevertheless, the ongoing outbreak involving eastern DRC and Uganda has renewed international concern because no licensed vaccine has demonstrated proven efficacy against the Bundibugyo virus, and currently approved monoclonal antibody therapies were developed primarily against Zaire Ebolavirus. Consequently, understanding the molecular biology of Bundibugyo virus has become an urgent priority for improving outbreak preparedness and guiding the development of species-specific or broadly protective countermeasures.[4]

The Ebolavirus genome is a remarkably efficient genetic system that encodes only seven structural proteins, yet these proteins coordinate highly sophisticated mechanisms of viral replication, immune evasion, host adaptation, and virion assembly. Detailed characterization of viral genome organization and replication has revealed several potential therapeutic targets, including the viral glycoprotein (GP), RNA-dependent RNA-polymerase (RdRp or L protein), nucleoprotein (N), and interferon antagonists VP24 and VP35. These advances have also clarified why genetic differences between Ebolavirus species can profoundly influence vaccine efficacy and antibody-mediated protection.[5,6]

CLASSIFICATION OF EBOLAVIRUSES

Members of the genus *Orthoebolavirus* are enveloped, filamentous viruses possessing a non-segmented, negative-sense single-stranded RNA genome. Six species are currently recognized, namely, *Zaire Ebolavirus*, *Sudan Ebolavirus*, *Bundibugyo Ebolavirus*, *Taï Forest Ebolavirus*, *Reston Ebolavirus*, and *Bombali Ebolavirus*.[7]

Among these, Zaire, Sudan, and Bundibugyo viruses are responsible for almost all confirmed human outbreaks. Reston virus causes disease in non-human primates and pigs but has not been associated with symptomatic human infection, whereas Bombali virus has so far been detected primarily in bats. Fruit bats are considered the principal natural reservoir, from which spillover into humans may occur directly or through intermediate mammalian hosts.[8]

GENOME ORGANIZATION OF EBOLAVIRUS

The Ebolavirus genome consists of approximately 18.9 kb of linear, non-segmented, negative-sense RNA, containing seven sequentially arranged structural genes (Figure 1). These genes are flanked by highly conserved leader and trailer regions that regulate transcription and replication.

Unlike many DNA viruses, Ebolavirus carries its own RdRp because host cells cannot directly translate negative-sense RNA genomes. Each gene is separated by conserved transcription initiation and termination signals, enabling sequential transcription by the viral polymerase. Because transcription proceeds from the 3′ end toward the 5′ terminus, genes located nearest the promoter, particularly NP, are expressed at the highest levels, producing a characteristic transcriptional gradient.[9,10]

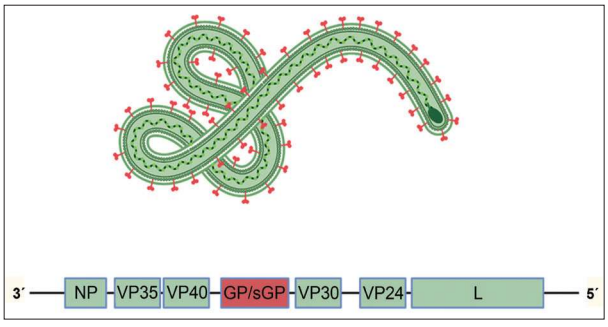


Figure 1: Ebolavirus genome organization'

The GP gene represents one of the most distinctive features of the Ebolavirus genome. Through transcriptional RNA editing, a single

GP gene generates multiple protein products, including the membrane glycoprotein ($GP_{1,2}$), soluble glycoprotein (sGP), and small soluble glycoprotein (ssGP). This strategy enables the virus simultaneously to mediate cellular entry while modulating host immune responses.[11]

FUNCTIONS OF INDIVIDUAL VIRAL PROTEINS

Nucleoprotein (NP): This encapsidates viral genomic RNA to form the ribonucleoprotein (RNP) complex. NP protects viral RNA from degradation and provides the structural scaffold required for transcription and genome replication.[12] NP also interacts extensively with VP35, VP30, and RdRp (L protein) to regulate replication complex assembly.[13]

VP35: This is a multifunctional phosphoprotein that serves as an essential polymerase cofactor while simultaneously acting as one of the virus's principal interferon antagonists.[14] By inhibiting activation of RIG-I-like receptors and downstream interferon signaling pathways, VP35 suppresses innate antiviral immunity, thereby facilitating efficient viral replication during the earliest stages of infection.[15]

VP40: This constitutes the major viral matrix protein responsible for virion assembly and budding. Remarkably, expression of VP40 alone in cultured cells can generate virus-like particles (VLPs) that closely resemble authentic Ebola virions morphologically.[16] VP40 coordinates interactions between nucleocapsids and the host plasma membrane, ultimately driving release of mature infectious particles.[17]

Glycoprotein: This is the only viral protein exposed on the virion surface and therefore represents the principal target for neutralizing antibodies and vaccine development. GP mediates attachment to host cells, endosomal fusion, and viral entry. The extensive glycosylation of GP also shields critical epitopes from antibody recognition, contributing to immune evasion.[18] Furthermore, abundant secretion of soluble GP may divert host antibody responses away from membrane-bound GP expressed on infectious virions.[19]

VP30: This functions primarily as a transcription activator. It regulates initiation of viral mRNA synthesis by interacting with NP and the RNA polymerase complex. Phosphorylation-dependent regulation of VP30 provides an important molecular switch controlling the balance between viral transcription and genome replication.[20,21]

VP24: This contributes both to nucleocapsid maturation and immune evasion. One of its most important functions is inhibition of interferon signalling through blockade of STAT1 nuclear translocation.[22] Consequently, infected cells become markedly less responsive to type I interferons, permitting sustained viral replication despite activation of innate immune responses.

L Protein: This is the largest viral protein and functions as the RdRp. Besides RNA synthesis, L protein possesses enzymatic activities required for mRNA capping, methylation, and polyadenylation, thereby enabling efficient translation of viral proteins by host ribosomes.[23,24]

REPLICATION CYCLE OF EBOLAVIRUS

Replication occurs entirely within the cytoplasm of infected cells and involves a highly coordinated sequence of events (Figure 2).

Attachment and Entry

Viral infection begins with attachment of GP to multiple host attachment factors, including C-type lectins, TIM-1, and phosphatidylserine receptors. Internalization occurs predominantly through macropinocytosis, after which virions traffic to late endosomes.[25] Within endosomes, host cathepsins B and L cleave GP, exposing receptor-binding domains that interact with the essential intracellular receptor Niemann-Pick C1 (NPC1).[26] This interaction triggers membrane fusion and releases the viral nucleocapsid into the cytoplasm.

Transcription

Following uncoating, the viral RdRp initiates transcription of individual viral genes. Because the genome is a negative-sense RNA, positive-sense mRNAs must first be synthesized before protein translation can occur. Sequential transcription produces progressively lower expression of downstream genes owing to attenuation at gene junctions.[9,10]

Genome Replication

Once sufficient NP accumulates, the viral polymerase shifts from transcription to genome replication, producing full-length positive-sense antigenomes that subsequently serve as templates for synthesis of new genomic RNA molecules. Newly synthesized genomes are immediately encapsidated by NP, preventing degradation and facilitating nucleocapsid assembly.[27]

Assembly and Budding

Viral nucleocapsids migrate to the plasma membrane, where VP40 orchestrates assembly with GP-containing membranes. Budding of mature virions occurs through host ESCRT (Endosomal Sorting Complex Required for Transport) machinery, after which infectious particles are released to initiate subsequent rounds of infection.[28,29]

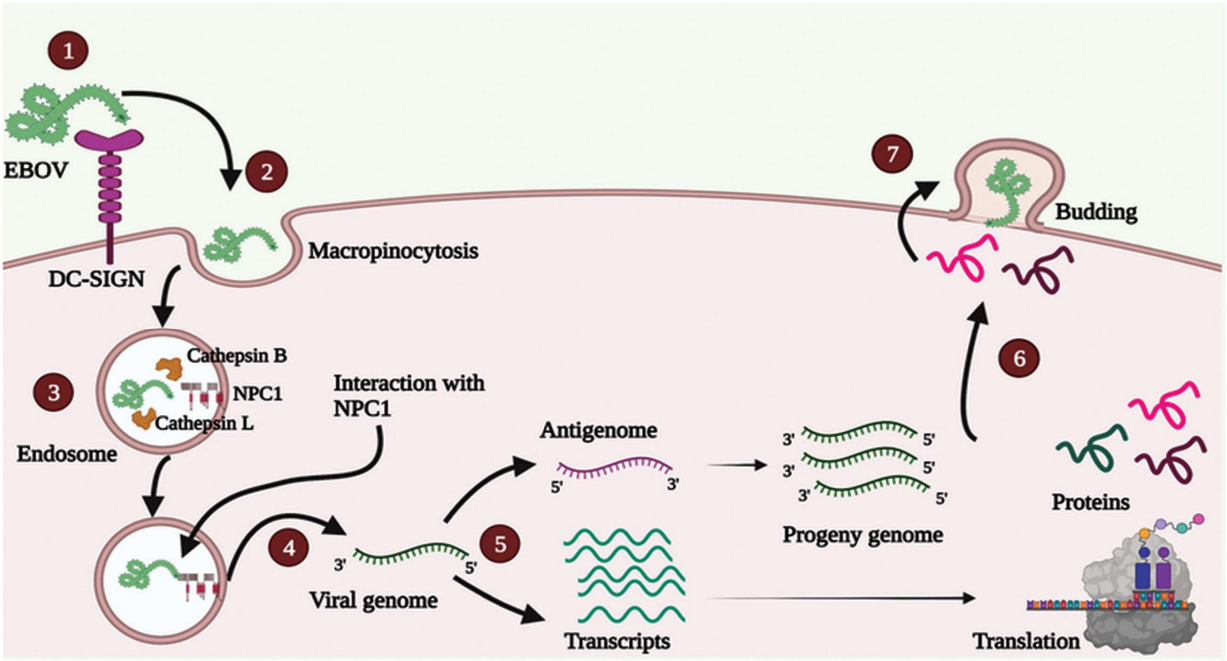


Figure 2: Replication cycle of Ebolavirus

GENOMIC DIVERSITY OF EBOLAVIRUSES

Although all members of the genus *Orthoebolavirus* share a common genomic organization (3′–NP–VP35–VP40–GP–VP30–VP24–L–5′), they exhibit considerable nucleotide and amino acid sequence diversity. Comparative genomic analyses demonstrate that the GP, VP24, VP35, and, to a lesser extent, the L protein (RdRp) accumulate mutations that influence host tropism, pathogenicity, immune escape, and susceptibility to antibody-mediated neutralization.[30]

Among the pathogenic human Ebolaviruses, Zaire Ebolavirus and Bundibugyo virus differ by approximately one-third of their genomic sequence. This level of divergence is substantial for viruses whose principal vaccine target is a surface GP. Consequently, although the overall genome architecture remains conserved, the antigenic landscapes of the two viruses differ sufficiently to reduce cross-protective immunity.[31]

Phylogenetic analyses indicate that Bundibugyo virus occupies a distinct evolutionary lineage between Zaire and Sudan Ebolaviruses. These evolutionary differences are reflected in variations in receptor-binding domains, glycan cap architecture, mucin-like domains, and neutralizing antibody epitopes of the viral glycoprotein.[32,33]

GLYCOPROTEIN GENE: THE PRINCIPAL BARRIER TO VACCINE DEVELOPMENT

The GP gene is the single most important determinant of vaccine efficacy because virtually all currently licensed Ebola vaccines

induce protective immunity by expressing the viral surface GP.

Unlike many viral antigens, Ebolavirus GP is heavily glycosylated and structurally complex. The mature GP exists as a trimer comprising GP_1 and GP_2 subunits linked by disulphide bonds. GP_1 mediates receptor recognition, whereas GP_2 facilitates membrane fusion following endosomal entry.[34] The GP gene also undergoes transcriptional RNA editing, generating three principal products, namely, membrane glycoprotein ($GP_{1,2}$), soluble glycoprotein (sGP), and small soluble glycoprotein (ssGP).[35]

This RNA-editing strategy represents a sophisticated immune evasion mechanism. Soluble GP is secreted in large quantities into the circulation and can bind circulating antibodies, thereby acting as an immunological decoy. Consequently, a proportion of antibodies generated during natural infection or vaccination may be diverted away from membrane-bound GP expressed on infectious virions.[36]

CURRENT VACCINE PLATFORMS AGAINST EBOLAVIRUS

Primarily, five vaccine technologies for Ebolavirus have been investigated so far, which are highlighted below and depicted in Figure 3.

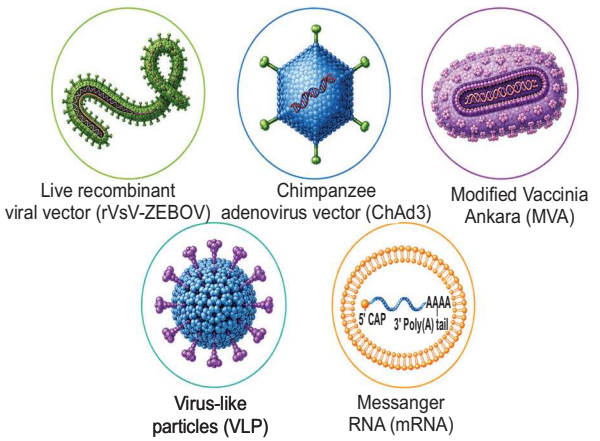


Figure 3: Major vaccine platforms for Ebolavirus

Live Recombinant Viral Vectors

The most successful platform remains recombinant vesicular stomatitis virus (rVSV) expressing Zaire Ebola GP (rVSV-ZEBOV), which demonstrated high efficacy during outbreaks caused by Zaire ebolavirus.[37]

Chimpanzee Adenovirus Vectors

Chimpanzee adenovirus type 3 (ChAd3)-based vaccines induce robust cellular and humoral immunity and have shown promising immunogenicity in early clinical studies.[38]

Modified Vaccinia Ankara (MVA) Boosters

Prime-boost regimens combining adenoviral vectors with MVA have demonstrated enhanced durability of immune responses.[39]

Virus-like Particles (VLPs)

VLP vaccines reproduce the structural organization of Ebola virions without containing infectious genetic material. These vaccines generate strong antibody responses in animal models but require further clinical evaluation.[40]

Messenger RNA (mRNA) Vaccines

Building upon the success of COVID-19 vaccine technology, several multivalent mRNA vaccine candidates targeting multiple Ebolavirus species are currently under preclinical and early clinical development. Such vaccines may provide a promising strategy for protecting against Bundibugyo virus and other emerging Ebolaviruses.[41,42]

WHY THE BUNDIBUGYO VIRUS GENOME COMPLICATES VACCINE DEVELOPMENT

Antigenic Divergence from Zaire Ebolavirus

The greatest challenge arises from the marked amino acid differences between the GP of Bundibugyo virus and Zaire Ebolavirus. The licensed recombinant vesicular stomatitis virus vaccine (rVSV-ZEBOV) expresses only the GP of Zaire Ebolavirus. Protection afforded by this vaccine depends largely on antibodies directed against conformational epitopes present on Zaire GP. However, several of these epitopes are absent, structurally altered, or only partially conserved in Bundibugyo virus. As a consequence, antibodies induced by Zaire-specific vaccines exhibit substantially reduced neutralizing activity against Bundibugyo virus in experimental systems.

Although some cross-reactive antibodies exist, their breadth and potency appear insufficient to guarantee reliable clinical protection during large outbreaks, such as the present 2026 outbreak.[43,44]

Extensive Glycan Shielding

The GP of Bundibugyo virus possesses extensive N-linked and O-linked glycosylation within its mucin-like domain.[45] These carbohydrate structures form a glycan shield that masks underlying protein epitopes from neutralizing antibodies.[46] Minor alterations in glycosylation patterns between Ebolavirus species can profoundly influence antibody accessibility without altering receptor-binding capacity. Therefore, even modest genomic differences may produce substantial antigenic variation.

Species-specific Neutralizing Antibodies

Protective immunity against Ebolavirus depends largely upon neutralizing antibodies recognizing highly specific conformational epitopes. Numerous monoclonal antibodies were developed following the West African epidemic. These were incorporated into licensed antibody cocktails, which were selected using Zaire Ebolavirus GP. Many demonstrate diminished affinity for Bundibugyo GP because mutations alter the three-dimensional structure of antibody-binding surfaces.[47] Consequently, therapeutic antibodies highly effective against Zaire Ebolavirus cannot automatically be assumed to protect against Bundibugyo virus.

Genetic Plasticity During Outbreaks

Although Ebolaviruses evolve considerably more slowly than influenza viruses, prolonged human-to-human transmission permits progressive accumulation of mutations. Most mutations are selectively neutral, but occasional amino acid substitutions occur within GP receptor-binding domains, antibody epitopes, polymerase-associated proteins, and interferon antagonists. Continuous genomic sequencing during outbreaks is therefore essential for detecting variants that could influence transmissibility, pathogenicity, or immune recognition.[48]

Limited Clinical and Experimental Data

A major obstacle to vaccine development is the relative rarity of Bundibugyo outbreaks. Compared with Zaire Ebolavirus, far fewer viral genomes have been sequenced and only a limited number of animal challenge studies have been completed. Also, correlates of protective immunity remain poorly defined and clinical efficacy data for candidate vaccines are lacking. Consequently, vaccine developers possess substantially less immunological information on Bundibugyo virus than on Zaire virus.[49]

IMMUNE EVASION STRATEGIES OF BUNDIBUGYO VIRUS

Like other Ebolaviruses, Bundibugyo virus has evolved multiple mechanisms to suppress innate and adaptive immune responses, which are highlighted below:

VP35-mediated Inhibition of Interferon Production

VP35 binds double-stranded RNA intermediates generated during replication, thereby preventing activation of RIG-I and MDA5 signaling pathways. Suppression of interferon production allows unrestricted viral replication during the earliest phase of infection.[50]

VP24-mediated Blockade of Interferon Signaling

VP24 interferes with nuclear import of phosphorylated STAT1 by binding karyopherin-α proteins. Consequently, infected cells become refractory to interferon-mediated antiviral responses.[22]

Lymphocyte Apoptosis

Although lymphocytes are generally not directly infected, extensive apoptosis of T-cells and B-cells occurs through indirect inflammatory mechanisms, contributing to profound immunosuppression and impaired adaptive immunity.[2]

Cytokine Dysregulation

Infected monocytes and macrophages release excessive concentrations of inflammatory mediators, including TNF-α, IL-6, and other

cytokines. This dysregulated inflammatory response contributes to vascular leakage, disseminated intravascular coagulation, and multiorgan failure characteristic of severe Ebolavirus disease.[51]

TOWARDS BROADLY PROTECTIVE PAN-EBOLAVIRUS VACCINES

The limitations of species-specific vaccines have shifted research toward pan-ebolavirus vaccine development. Several complementary approaches are being explored.

- Incorporation of GPs from multiple Ebolavirus species into a single vaccine formulation.
- Identification of highly conserved neutralizing epitopes shared across Ebolaviruses.
- Structure-guided immunogen design targeting conserved GP stem regions.
- Mosaic nanoparticle vaccines displaying GPs from multiple species.
- Multivalent mRNA vaccine platforms encoding antigens from Zaire, Sudan, and Bundibugyo viruses simultaneously.

Broadly protective vaccines could substantially improve preparedness against future outbreaks caused by previously neglected Ebolavirus species.[52,53]

IMPLICATIONS FOR THE CURRENT BUNDIBUGYO VIRUS OUTBREAK

The genomic characteristics of Bundibugyo virus have profound implications for the ongoing outbreak in the DRC and Uganda. First, the absence of a licensed BDBV-specific vaccine means that ring vaccination strategies cannot be implemented with the same confidence as during Zaire Ebolavirus outbreaks. Second, uncertainty regarding the effectiveness of existing monoclonal antibody therapies complicates clinical management. Third, continued viral evolution during sustained transmission underscores the importance of real-time genomic surveillance to identify mutations that may influence diagnostic assay performance, antiviral susceptibility, or immune recognition. Finally, the outbreak highlights the urgent need for international investment in broadly protective vaccines and therapeutics that extend beyond Zaire Ebolavirus and address the full diversity of pathogenic Ebolaviruses.

FUTURE RESEARCH PRIORITIES

The present outbreak has identified several urgent research priorities, which are highlighted below.

1. Development of multivalent or pan-ebolavirus vaccines providing protection against Zaire, Sudan, Bundibugyo, and other pathogenic Ebolaviruses.
2. Discovery of broadly neutralizing monoclonal antibodies targeting highly conserved GP epitopes.
3. Expansion of real-time genomic surveillance throughout Central and East Africa.
4. Identification of immunological correlates of protection against Bundibugyo virus.
6. Improved understanding of viral persistence, post-ebola sequelae, and long-term transmission dynamics.
7. Development of rapid point-of-care molecular diagnostics suitable for resource-limited settings.
8. Strengthening of regional clinical trial platforms capable of rapidly evaluating candidate vaccines and therapeutics during future outbreaks.

CONCLUSION

The compact genome of Ebolavirus encodes a highly efficient molecular machinery that enables rapid replication while simultaneously suppressing innate and adaptive immune responses. Advances in molecular virology have greatly improved understanding of Ebolavirus genome organization, replication, and host-pathogen interactions, leading to important progress in diagnostics, therapeutics, and vaccine development. Nevertheless, the ongoing Bundibugyo virus outbreak in the Democratic Republic of Congo has exposed major gaps in global preparedness. The substantial genetic divergence of the Bundibugyo virus GP from that of Zaire Ebolavirus limits the expected effectiveness of currently licensed vaccines and monoclonal antibody therapies, emphasizing the urgent need for broadly protective pan-ebolavirus

counter measures.

Beyond its virological significance, the outbreak illustrates how armed conflict, fragile health systems, delayed case recognition, population mobility, and community mistrust can amplify epidemic spread despite advances in biomedical science. Future preparedness should therefore combine sustained investment in genomic surveillance, integrated One Health surveillance, strengthened laboratory and clinical infrastructure, accelerated development of multivalent vaccines and therapeutics, and enhanced international collaboration. Addressing these scientific and operational challenges will be essential to reducing the impact of future Ebola outbreaks and strengthening global health security.

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