

Molecular Evasion and Immune Responses to Ebola Virus- an Approach to Ebola Evasion Mechanism and Immunotherapeutic

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ABSTRACT

Ebola virus (EBOV; species Zaire ebolavirus, family Filoviridae) causes Ebola virus disease (EVD), a severe hemorrhagic fever of humans and non-human primates with case fatality rates that have ranged from 25% to 90% in past outbreaks. The 2013–2016 West African epidemic — more than 28,600 cases and 11,325 deaths — transformed EVD from a neglected zoonosis into a test case for modern vaccinology, immunotherapeutics and outbreak science. This review integrates current understanding of the molecular biology of EBOV with the host immune response it provokes. We describe the 18.9-kb negative-sense RNA genome and its seven genes; the architecture of the filamentous virion; and the replication cycle, from glycoprotein-mediated attachment and Niemann–Pick C1-dependent endosomal fusion to VP40-driven assembly and budding. We then examine the virus's multi-layered interference with innate immunity — VP35-mediated blockade of interferon induction, VP24-mediated blockade of interferon signaling, and glycoprotein-based shielding, decoy and counter-tetherin strategies — and show how these mechanisms shape the systemic immunopathology of EVD: abrupt activation of monocytes and macrophages, a dysregulated "cytokine storm", bystander lymphocyte apoptosis, dendritic-cell failure, coagulopathy and vascular leakage. Correlates of survival — early humoral responses, controlled inflammation and timely T-cell immunity — are contrasted with the signatures of fatal disease. Finally, we review the countermeasure landscape built on this knowledge: the rVSV-vectored vaccine Ervebo, the Ad26/MVA-BN-Filo regimen, the monoclonal-antibody therapeutics ansuvimab (mAb114) and REGN-EB3 validated in the PALM randomized trial, and the remaining gaps for Sudan, Bundibugyo and other ebolaviruses — thrown into sharp relief by the 2025–2026 outbreaks in the Democratic Republic of the Congo. Understanding the molecular dialogue between EBOV and the immune system remains the foundation for the next generation of pan-filovirus vaccines and therapeutics.

Keywords: Ebola virus; Filoviridae; glycoprotein; VP35; VP24; interferon antagonism; cytokine storm; monoclonal antibody; rVSV-ZEBOV; vaccine; immune evasion

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1. INTRODUCTION

Ebola virus disease (EVD) first came to medical attention in 1976, when two near-simultaneous outbreaks of a severe hemorrhagic fever struck the village of Yambuku in Zaire (now the Democratic Republic of the Congo, DRC) and the

district of Nzara in southern Sudan.^[1] The causative agents were shown to be two related but distinct filamentous viruses, later designated Ebola virus (EBOV) and Sudan virus (SUDV). Over the following four decades, EVD recurred in more than two dozen outbreaks across equatorial Africa, with case fatality rates varying between roughly 25% and 90% depending on the viral species, the setting and the quality of supportive care.^{[1], [2]}

The epidemic that began in Guinea in December 2013 and spread through Sierra Leone and Liberia until 2016 dwarfed all previous events: more than 28,600 confirmed, probable and suspected cases and 11,325 deaths were recorded, and the virus reached cities, crossed borders and seeded cases on three other continents.^{[3], [4]} Genomic surveillance demonstrated that the epidemic originated from a single zoonotic introduction followed by sustained human-to-human transmission, and that viral evolution during the epidemic generated lineages with altered glycoprotein biology.^[4] The epidemic also catalyzed an unprecedented acceleration of countermeasure development: a recombinant vesicular stomatitis virus–vectored vaccine was tested in a ring-vaccination trial in Guinea while the epidemic was still ongoing,^[5] and monoclonal-antibody therapeutics were advanced from animal studies to a randomized controlled trial during the 2018–2020 DRC outbreak.^[6] EVD remains a recurrent threat. The DRC experienced its sixteenth outbreak in Kasai Province in late 2025, and 2026 brought a further large outbreak caused by Bundibugyo virus — an ebolavirus species for which no licensed vaccine or therapeutic exists.^{[7], [8]} The biological basis of EVD severity lies in an intimate molecular conflict: EBOV encodes a compact set of proteins that dismantle the host's interferon system and misdirect the immune response, while the speed, magnitude and quality of the host's counter-response largely determine survival. This review traces that conflict from the molecular to the systemic level, and from basic mechanisms to the vaccines and antibody therapeutics that exploit them.

Taxonomy, Ecology and Genome Organization

Ebolaviruses belong to the family *Filoviridae* (from Latin *filum*, "thread"), order *Mononegavirales* — the non-segmented negative-sense RNA viruses. Taxonomic revisions have defined six species within the genus *Ebolavirus*: *Zaire ebolavirus* (Ebola virus, EBOV), *Sudan ebolavirus* (SUDV), *Tai Forest ebolavirus* (TAFV), *Bundibugyo ebolavirus* (BDBV), *Reston ebolavirus* (RESTV) and *Bombali ebolavirus* (BOMV).^[9] The genus *Marburgvirus* and the more distant *Cuevavirus*, *Dianlovirus*, *Striavirus* and *Thamnovirus* genera complete the family. The six ebolavirus species differ substantially in human virulence and in the availability of countermeasures (Table 1): every licensed vaccine and antibody therapeutic targets EBOV alone.^{[2], [8]}

Table 1. The six species of the genus *Ebolavirus*. CFR, case fatality rate; DRC, Democratic Republic of the Congo.

Species (virus)	First recognized	Notable outbreaks / detections	Reported CFR in humans
<i>Zaire ebolavirus</i> (EBOV)	1976, Yambuku, DRC	West Africa 2013–2016 (>28,600 cases); DRC 2018–2020 (>3,400 cases); Kasai, DRC 2025	≈ 50–90% (outbreak- and care-dependent)
<i>Sudan ebolavirus</i> (SUDV)	1976, Nzara, South Sudan	Uganda 2000–2001 (425 cases), 2011, 2022, 2025	≈ 41–65%
<i>Bundibugyo ebolavirus</i> (BDBV)	2007, Bundibugyo, Uganda	DRC 2012; DRC 2026 (ongoing at the time of writing)	≈ 25–36%
<i>Tai Forest ebolavirus</i> (TAFV)	1994, Tai National Park, Côte d'Ivoire	Single documented human case (non-fatal), linked to a chimpanzee necropsy	Not established (one non-fatal case)
<i>Reston ebolavirus</i> (RESTV)	1989, Reston, Virginia, USA	Epizootics in imported macaques; pigs in the Philippines; asymptomatic human seroconversions	No human disease documented
<i>Bombali ebolavirus</i> (BOMV)	2018, Sierra Leone / Guinea / Kenya	Detected only in insectivorous bats; no human infection known	Unknown

Ebolaviruses are zoonotic. Epidemiological and serological evidence implicates fruit bats as a major reservoir: viral RNA

and antibodies have been detected in several fruit-bat species that survive experimental infection without disease, and index cases of human outbreaks are frequently linked to contact with bats, great apes or other wildlife.^[10] Human-to-human transmission then occurs through direct contact with blood, secretions or contaminated materials, with viral loads peaking late in illness and remaining high after death — the basis of burial-associated transmission.^[1]

2. GENOME ORGANIZATION

The EBOV genome is a single molecule of negative-sense, non-segmented RNA of approximately 18.9 kb, tightly encapsidated by the nucleoprotein (NP). Seven genes are arranged in the invariant order 3'-NP-VP35-VP40-GP-VP30-VP24-L-5', flanked by a 3' leader and a 5' trailer that contain the signals for replication and transcription (Figure 1).^[1]^[11] Each gene is transcribed from its own conserved start and stop signals, yielding seven monocistronic, capped and polyadenylated mRNAs; transcriptional attenuation at each gene junction produces a 3'→5' gradient in which NP is the most abundant transcript and L the least.^[11]

A remarkable feature of the GP gene is co-transcriptional RNA editing. The unedited GP mRNA encodes the secreted glycoprotein sGP — the most abundant GP-gene product — whereas insertion of a non-templated cytosine residue by polymerase "stuttering" at a run of seven uridines shifts the reading frame and yields the full-length membrane glycoprotein GP₀, the precursor of the virion surface spike; a further editing product, ssGP, is made in smaller amounts.^[12] This economical arrangement lets a single gene produce both a decoy molecule (sGP) and the structural fusion protein (GP_{1,2}), a division of labor central to immune evasion (Section 5).

Ebola virus genome — non-segmented negative-sense ssRNA (≈ 18.9 kb); gene order 3'-NP-VP35-VP40-GP-VP30-VP24-L-5'

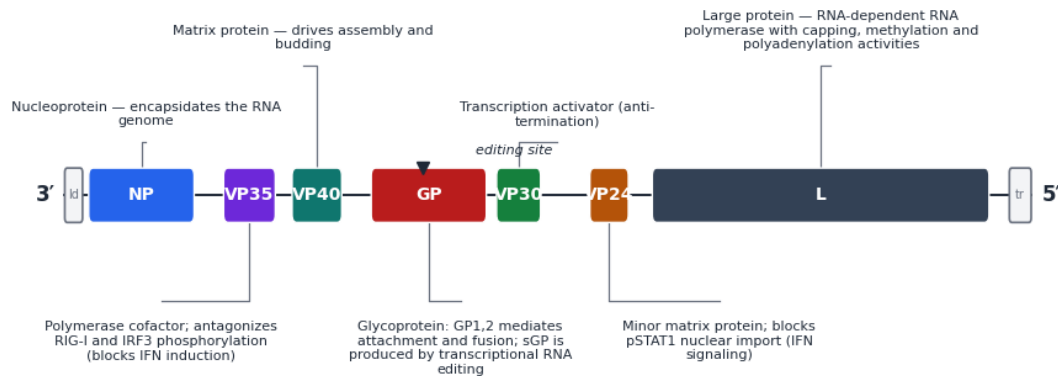


Figure 1. Organization of the ≈ 18.9-kb Ebola virus genome. Seven genes (colored blocks, drawn approximately to scale) lie between the 3' leader (ld) and 5' trailer (tr); black bars denote intergenic regions. The arrowhead marks the co-transcriptional editing site in the GP gene, at which polymerase stuttering inserts an extra cytosine to switch expression from the secreted glycoprotein sGP to the membrane glycoprotein GP_{1,2}. Principal protein functions are annotated.

Virion Architecture

Filovirions are among the most morphologically distinctive of all virus particles: enveloped, filamentous and strikingly pleomorphic, appearing under the electron microscope as rods, circles, "6"-shaped or "U"-shaped forms and the classical "shepherd's crook", with a uniform diameter of ≈ 80 nm and lengths approaching 1,000 nm (Figure 2).^[1] The particle is built from the inside out. At its core lies the ribonucleoprotein (RNP) complex: the genomic RNA helically encapsidated by NP, together with the polymerase cofactor VP35, the transcription activator VP30, the minor matrix protein VP24 and the large (L) RNA-dependent RNA polymerase. Surrounding the RNP is a matrix layer formed by VP40 — the principal structural driver of particle assembly and shape — associated with the inner leaflet of a host-derived lipid bilayer. Embedded in the envelope are trimeric spikes of the glycoprotein GP_{1,2}, the sole viral surface protein and the principal target of neutralizing antibodies.^[11]^[13]

VP40 is a structural transformer: it can adopt a dimeric form that traffics to the plasma membrane, a ring-shaped octamer that binds RNA and regulates viral transcription, and a filament-forming hexamer that builds the matrix layer and drives budding — a single protein encoding three distinct functions through conformational rearrangement.^[14] The GP spike is likewise multifunctional: each trimer consists of three GP₁–GP₂ heterodimers generated by furin cleavage of GP₀, with GP₁ carrying the receptor-binding, glycan-cap and heavily glycosylated mucin-like domains and GP₂ anchoring the trimer in the membrane and executing membrane fusion.^[13]

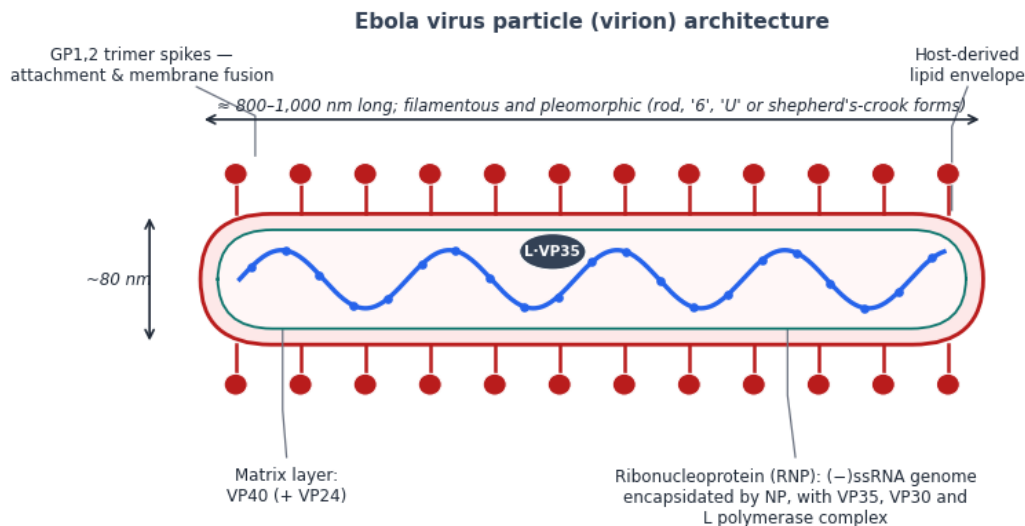


Figure 2. Architecture of the Ebola virion. Trimeric GP_{1,2} spikes protrude from a host-derived lipid envelope; beneath it, the VP40 matrix layer (with VP24) encases the helical ribonucleoprotein — the (–)ssRNA genome encapsidated by NP and associated with the L·VP35 polymerase complex and VP30. Virions are ≈ 80 nm in diameter, filamentous and pleomorphic.

3. THE VIRAL LIFE CYCLE

Attachment and entry

EBOV displays broad cellular tropism, infecting monocytes, macrophages and dendritic cells early in infection and hepatocytes, adrenal cortical cells, fibroblasts and epithelial cells as disease advances; notably, lymphocytes are not productively infected — a fact with major immunological consequences (Section 7).^[1] Entry is a two-stage process (Figure 3). First, GP_{1,2} engages attachment factors that concentrate virions on the cell surface, including C-type lectins (DC-SIGN/L-SIGN) on dendritic cells and macrophages, phosphatidylserine receptors of the TIM and TAM families, and cell-surface glycosaminoglycans.^{[11], [15]} Second, the particle is internalized by macropinocytosis into the endosomal compartment, where the decisive molecular events occur: endosomal cathepsins B and L cleave GP₁, stripping away the glycan cap and mucin-like domain to expose the receptor-binding core;^[16] the cleaved GP then binds its essential intracellular receptor, the cholesterol transporter Niemann–Pick C1 (NPC1), in the late endosome/lysosome;^[17] and this engagement triggers the GP₂ fusion machinery, which inserts its internal fusion loop into the endosomal membrane and drives fusion, releasing the RNP into the cytoplasm. The requirement for NPC1 was demonstrated by haploid genetic screening and validated in NPC1-deficient cells and animals, identifying a host factor now exploited as a drug target.^[17]

Transcription and replication

In the cytoplasm, the encapsidated genome serves as template for the L·VP35 polymerase. Primary transcription generates the seven mRNAs without requiring *de novo* protein synthesis; efficient transcription of the NP gene, and thus of all downstream genes, requires VP30-dependent anti-termination at a stem–loop structure in the NP 5' untranslated region.^[11] As NP accumulates, the polymerase switches to genome replication: synthesis of a full-length complementary positive-sense antigenome, which in turn templates progeny negative-sense genomes that are co-translationally encapsidated by NP. Replication occurs in perinuclear cytoplasmic inclusion bodies — viral factories visible by light microscopy.^[1]

Assembly, budding and egress

GP₀ is synthesized on membrane-bound ribosomes, extensively N- and O-glycosylated in the endoplasmic reticulum and Golgi, cleaved by furin into GP₁ and GP₂, and transported as trimers to plasma-membrane lipid rafts.^[13] VP40 oligomers recruit RNP complexes and GP_{1,2}-containing membrane patches; the VP40 late-domain motifs hijack the host ESCRT machinery to pinch off filamentous particles.^[14] Budding is opposed by the host restriction factor tetherin (BST-2), which physically tethers nascent enveloped virions to the cell surface — a blockade that the EBOV glycoprotein, unusually, is able to counteract.^[18] The cycle is completed in hours, and a single infected macrophage can release thousands of particles, feeding the exponential viremia of acute EVD.

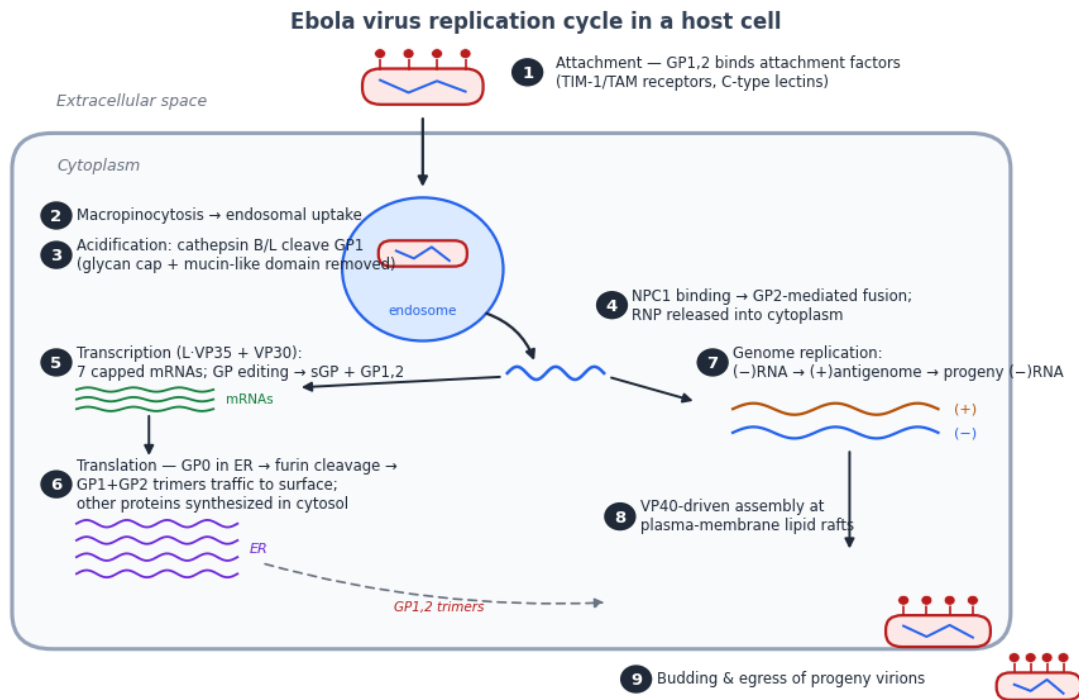


Figure 3. The Ebola virus replication cycle. (1) GP_{1,2}-mediated attachment to cell-surface factors; (2) macropinocytic uptake; (3) endosomal acidification and cathepsin B/L cleavage of GP₁; (4) NPC1 binding and GP₂-driven fusion, releasing the RNP; (5) primary transcription of seven mRNAs, including editing of the GP transcript; (6) translation — GP₀ is processed in the ER and furin-cleaved, while the remaining proteins are made on free ribosomes; (7) genome replication through a full-length antigenome intermediate; (8) VP40-driven assembly at plasma-membrane lipid rafts; (9) budding and egress.

Molecular Mechanisms of Immune Evasion

The defining feature of EBOV immunobiology is the systematic sabotage of the type-I interferon (IFN- α/β) system by two viral proteins, VP35 and VP24, complemented by a third layer of glycoprotein-based deception at the cell surface (Figure 4).^{[11], [23]}

VP35: blocking interferon induction

Recognition of viral double-stranded RNA by the cytosolic sensors RIG-I and MDA5 normally triggers a signaling cascade through MAVS and the kinases TBK1/IKK ϵ , culminating in phosphorylation of IRF3 and IRF7, activation of NF- κ B and transcription of the IFN- α/β genes. EBOV VP35 was the first filovirus protein shown to function as a type-I IFN antagonist: its C-terminal interferon-inhibitory domain binds double-stranded RNA with high affinity, sequestering the pathogen-associated molecular pattern from RIG-I-like receptors, and simultaneously interacts with components of the induction machinery — including the RIG-I co-activator PACT and the IRF3 kinases — to prevent IRF3/IRF7 phosphorylation and IFN- β gene transcription.^{[19], [20]} Mutations that disrupt the VP35 dsRNA-binding surface render the virus attenuated, establishing IFN antagonism as a bona fide virulence mechanism.^[20] VP35 also moonlights as the essential polymerase cofactor (Section 4.2), elegantly coupling viral replication to innate immune suppression.

VP24: blocking interferon signaling

Even when IFN is produced by neighboring cells, EBOV-infected cells are deaf to it. IFN- α/β binding to IFNAR1/2 activates JAK1/TYK2 and the formation of the pSTAT1–pSTAT2–IRF9 (ISGF3) complex, which must be imported into the nucleus by karyopherin- α proteins to induce antiviral interferon-stimulated genes (ISGs). VP24 binds selectively to a non-classical nuclear-localization-signal binding site on karyopherin α 5, competitively displacing phosphorylated STAT1 and thereby trapping ISGF3 in the cytoplasm.^{[21], [22]} The result is a two-hit blockade — VP35 silences IFN production, VP24 silences IFN perception — that leaves the infected cell in an antiviral vacuum during the critical first days of infection.

The glycoprotein: shield, decoy and counter-restriction

At the cell and particle surface, GP_{1,2} protects the virus by camouflage and misdirection. Its dense glycan shield — the glycan cap and the heavily O-glycosylated mucin-like domain — covers conserved receptor-binding and fusion epitopes, so that most antibodies elicited by infection bind exposed, variable or non-neutralizing surfaces.^{[11], [13]} The abundant

secreted glycoprotein sGP shares the N-terminal epitopes of GP₁ and acts as an antigenic decoy, absorbing anti-GP antibodies in the bloodstream; sGP also modulates neutrophil and endothelial activation, contributing to the inflammatory disarray of EVD.^[12] In addition, surface-expressed GP sterically masks host molecules including MHC class I and β 1-integrins — a "cloak" that may impair recognition of infected cells — and, as noted above, antagonizes tetherin to ensure efficient virion release.^{[18], [23]} A soluble form of GP_{1,2} is further shed by the metalloprotease TACE, adding to the pool of circulating decoy antigen.^[11]

Molecular immune evasion by Ebola virus proteins

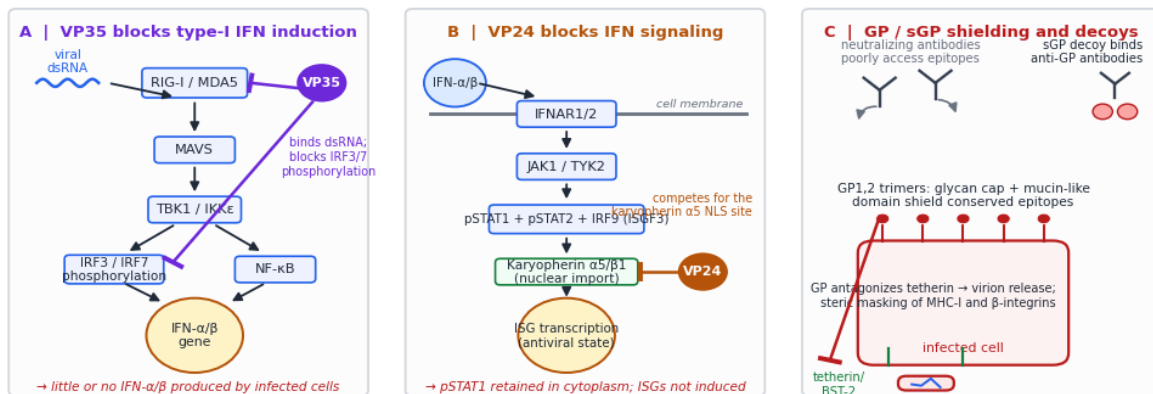


Figure 4. Molecular immune evasion by EBOV proteins. **A.** VP35 binds viral dsRNA and blocks IRF3/IRF7 phosphorylation, aborting IFN- α/β induction. **B.** VP24 competes with phosphorylated STAT1 for the nuclear-import receptor karyopherin α 5, blocking IFN signaling. **C.** GP_{1,2}'s glycan cap and mucin-like domain shield conserved epitopes from antibodies; shed sGP acts as an antibody decoy; and GP antagonizes the restriction factor tetherin while sterically masking MHC-I and integrins.

The Innate Immune Response

Target cells: infection without alarm

Monocytes, macrophages and dendritic cells (DCs) are the earliest and most important replication sites of EBOV. Because of the VP35/VP24 double blockade, these cells support vigorous viral replication while producing little or no IFN- α/β — the virus replicates "silently" at the very sentinels that should sound the alarm.^{[19], [23]} Infected DCs fail to mature: they up-regulate co-stimulatory molecules poorly, secrete abnormal cytokine profiles and are consequently unable to prime effective T-cell responses, undermining adaptive immunity at its origin.^{[23], [25]} Natural killer (NK) cells, whose activation depends in part on DC-derived signals, show impaired cytolytic function in fatal cases.^[25]

The macrophage-driven cytokine storm

Paradoxically, while the interferon axis is silenced, infected monocytes and macrophages become profusely — and pathologically — activated. Engagement of Toll-like receptor 4 by shed GP, together with viral replication itself, drives the release of TNF- α , IL-1 β , IL-6, IL-8, MCP-1 and other mediators in escalating quantities as viremia rises.^{[26], [27], [28]} This systemic inflammatory surge recruits and activates further monocytes, increases endothelial permeability and underlies the fever, malaise and gastrointestinal fluid losses of early EVD. High circulating levels of the immunoregulatory cytokine IL-10 and of the chemokine IP-10 are characteristic of severe and fatal disease.^{[26], [32]}

Coagulopathy and vascular leakage

The hemorrhagic manifestations that gave "Ebola hemorrhagic fever" its name are driven less by vascular infection than by coagulation failure. Infected monocytes and macrophages over-express tissue factor on their surface, triggering the extrinsic coagulation pathway, fibrin deposition and disseminated intravascular coagulation (DIC); primate studies identified monocyte/macrophage tissue-factor over-expression as a key event in EBOV coagulopathy.^[29] Consumption of clotting factors and platelets produces the mucosal bleeding, petechiae and oozing at venipuncture sites seen in a subset of patients. Endothelial cells are infected only late and inconsistently; the endothelial dysfunction and increased vascular permeability of EVD are largely indirect, mediated by the cytokine storm and by shed GP.^{[1], [11]} Necrosis of hepatocytes and adrenal cortical cells — direct viral targets — adds metabolic decompensation and impairs the synthesis of clotting factors and the stress response, culminating in distributive and hypovolemic shock.

The Adaptive Immune Response

Bystander lymphocyte apoptosis

One of the most striking features of fatal EVD is a profound loss of lymphocytes — despite the fact that EBOV does not productively infect them. Massive bystander apoptosis of CD4⁺ and CD8⁺ T cells and NK cells, driven by inflammatory

mediators (including TNF-related death-receptor pathways) and by the loss of DC support, empties lymphoid tissues in fatal cases.^{[25], [26]} The adaptive immune system is thus dismantled from without: the cells that would clear the virus are deleted before they can act.

Humoral responses

Antibody responses to EBOV follow two divergent trajectories. Patients destined to survive typically mount detectable virus-specific IgM within the first week of symptoms and robust, sustained IgG responses against GP (and NP) during the second week, coincident with viral clearance; anti-GP IgG can persist for years and likely protects against reinfection.^{[24], [26]} Fatal cases, by contrast, usually die before or just as an antibody response emerges, and when antibodies are detectable they are frequently non-neutralizing and directed at decoy or non-protective epitopes — consistent with the GP/sGP deception strategy (Section 5.3).^{[11], [25]} The therapeutic success of passively administered monoclonal antibodies (Section 9) provides the strongest functional proof that antibodies, when present early and of the right specificity, are decisive.

Cellular responses

Deep immunophenotyping of patients from the 2013–2016 epidemic overturned the older view that EVD is simply a state of immune paralysis: even fatal cases show substantial, sometimes extreme, T-cell activation.^[24] The difference lies in its quality and consequences. Survivors display early, moderate activation of CD8⁺ T cells with preserved T-cell counts and rapid contraction to memory; fatal cases show intense but uncoordinated activation accompanied by markers of exhaustion, collapsing lymphocyte numbers and absent antigen-specific effector function.^{[24], [30]} Transcriptomic studies of patient blood have distilled these observations into prognostic signatures: fatal outcome is associated with unrestrained expression of inflammatory and tissue-damage genes and suppressed antiviral and T-cell programs, while survivors resolve the inflammatory phase within the first two weeks.^{[30], [31]}

Protective versus Pathogenic Immunity: Determinants of Outcome

The immunology of EVD is a race between exponential viral replication and the assembly of an effective adaptive response, refereed by the innate system that EBOV has corrupted (Figure 5). Three variables recur across clinical cohorts as predictors of death: the baseline viral load, the duration of symptoms before care, and the magnitude of the inflammatory cytokine surge.^{[30], [32]} In a pediatric cohort, a panel of soluble mediators — including IL-10, IP-10, MCP-1 and markers of coagulopathy — discriminated fatal from non-fatal outcomes with high accuracy.^[32] The unique immune "signature" of EVD identified in Guinea combined hyperinflammation with features of T-cell exhaustion and monocyte deactivation (low HLA-DR), a profile more reminiscent of bacterial sepsis than of a typical antiviral response.^[30]

Survival, conversely, is characterized by: (i) a viral load contained early, implying that innate restriction — though blunted — is not abolished; (ii) an early-appearing IgM and IgG response against GP; (iii) controlled, self-limiting cytokine production; and (iv) functional EBOV-specific T cells that expand, clear infected cells and contract into memory.^{[24], [26]} Fatal disease is the mirror image: uncontrolled viremia feeding a self-amplifying cytokine storm, lymphocyte attrition, coagulopathy and shock, with death typically occurring around days 8–10 of symptoms. This framework directly explains clinical trial results: interventions that reduce viral load or supply ready-made neutralizing antibody are dramatically more effective when given early, and every additional day of delay before treatment measurably increases the odds of death (Section 9.3).^[6]

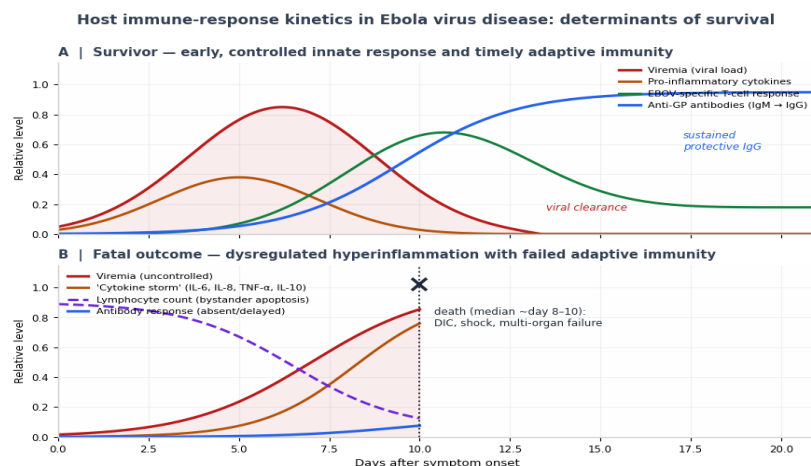


Figure 5. Schematic kinetics of viremia and immune responses in EVD. A. In survivors, a controlled cytokine response is followed within the first two weeks by EBOV-specific T cells and anti-GP antibodies, which clear the virus; antibody persists for years. **B.** In fatal cases, viremia rises unchecked, the cytokine response becomes a self-amplifying storm, lymphocytes are lost to bystander apoptosis, the antibody response fails to appear in time, and death ensues around days

8–10 from DIC, shock and multi-organ failure.

Vaccines and Immunotherapeutics

The countermeasures available today are direct products of the molecular immunology reviewed above: vaccines present GP_{1,2} to the immune system under conditions the virus itself never permits, and therapeutic antibodies supply, ready-made, the protective humoral response that fatal cases fail to generate (Figure 6, Table 2).

Vaccines

The leading vaccine, rVSV-ZEBOV (Ervebo), is a live, replication-competent vesicular stomatitis virus in which the VSV glycoprotein is replaced by EBOV GP — a decoy-proof presentation of the authentic entry protein. The platform was shown to protect non-human primates even under compressed, outbreak-relevant schedules,^[33] and depletion experiments established that GP-specific antibodies are necessary for the protection it confers.^[34] During the 2015 Guinea epidemic, an open-label, cluster-randomised ring-vaccination trial ("Ebola Ça Suffit!") vaccinated contacts and contacts-of-contacts of confirmed cases, randomizing clusters to immediate or delayed vaccination; no cases occurred from 10 days after vaccination among immediately vaccinated participants, indicating high efficacy.^{[5], [35]} Ervebo was approved by the European Medicines Agency and the US Food and Drug Administration in 2019 — the first licensed Ebola vaccine — and has since been deployed at scale: more than 300,000 people were vaccinated during the 2018–2020 DRC outbreak, and ring vaccination with Ervebo was again central to the response to the 2025 Kasai outbreak.^{[2], [7]} A second regimen, the heterologous two-dose Ad26.ZEBOV prime / MVA-BN-Filo boost (Zabdeno + Mvabea), was approved in Europe in 2020 on the basis of safety and immunogenicity data; the multivalent boost encodes GPs of EBOV, SUDV and Marburg virus plus TAFV nucleoprotein, anticipating broader species coverage.^{[2], [36]}

Monoclonal-antibody therapeutics

Antibody therapy evolved through three generations. ZMapp, a cocktail of three murine-human chimeric mAbs, first demonstrated that advanced EVD could be reversed therapeutically in non-human primates.^[37] mAb114 (ansuvimab) is a single fully human mAb cloned from a survivor of the 1995 Kikwit outbreak that targets the GP₁ head region and protects primates as monotherapy.^[38] REGN-EB3 is a three-mAb cocktail (atoltivimab, maftivimab, odesivimab) engineered to combine neutralizing and Fc-effector antibodies against non-overlapping GP epitopes.^[39] Systematic mapping of the anti-GP antibody response has since rationalized cocktail design: maximal protection requires antibodies that block entry *and* recruit immune effector functions against infected cells, with the GP₁ core and the GP₂ fusion machinery emerging as privileged targets.^[40]

The PALM trial: proof in patients

The Pamoja Tulinde Maisha ("Together Save Lives") trial, conducted during the 2018–2020 DRC outbreak, randomly assigned 681 patients to ZMapp (control), the antiviral remdesivir, mAb114 or REGN-EB3, all added to optimized supportive care. Both antibody therapeutics were significantly superior to ZMapp: 28-day mortality was 35.1% with mAb114 and 33.5% with REGN-EB3, versus 49.7% with ZMapp and 53.1% with remdesivir.^[6] The immunological logic of Section 8 was on full display: among patients presenting with low viral loads — those who reached care early — mortality fell to 9.9% (mAb114) and 11.2% (REGN-EB3), whereas patients with high viral loads still died in 64–70% of cases; each additional day of symptoms before admission raised the odds of death by $\approx 11\%$.^[6] Antibody therapeutics also accelerated viral clearance. On the strength of these data, REGN-EB3 (Inmazeb) and ansuvimab (Ebanga) became the first FDA-approved EVD therapeutics in 2020, and WHO's 2022 living guideline issued a strong recommendation for either agent in all patients with EBOV disease, alongside optimized supportive care.^{[2], [42]} The nucleotide-analogue prodrug remdesivir, which inhibits the viral L polymerase and fully protected rhesus macaques when given early after exposure,^[41] underperformed in PALM — a reminder that timing and mechanism must match the immunological stage of disease.

Remaining gaps

Every licensed countermeasure targets EBOV. For SUDV — which caused outbreaks in Uganda in 2022 and 2025 — and for BDBV, responsible for a large DRC outbreak in 2026, there are no approved vaccines or therapeutics; WHO-convened experts have prioritized candidate products, including the pan-ebolavirus antibody MBP134, the monoclonal antibody maftivimab and remdesivir, for evaluation in clinical trials during the Bundibugyo response.^[8] Broadly protective pan-filovirus vaccines and antibody cocktails, post-exposure prophylaxis, and thermostable formulations for remote settings remain the field's central engineering challenges.^{[8], [11]}

Table 2. Licensed medical countermeasures against Ebola virus (species *Zaire ebolavirus*). EMA, European Medicines Agency; FDA, US Food and Drug Administration; WHO PQ, WHO prequalification.

Product	Type	Platform / composition	First approval	Indication
Ervebo (rVSVΔG-ZEBOV-GP)	Live recombinant vaccine, single dose	VSV vector expressing EBOV GP _{1,2}	EMA & FDA 2019; WHO PQ	Prevention of EVD (pre-exposure and ring vaccination)
Zabdeno + Mvabea	Heterologous prime-boost vaccine, two doses	Ad26.ZEBOV prime; MVA-BN-Filo boost (EBOV, SUDV, MARV GPs + TAFV NP)	EMA 2020	Prevention of EVD
Inmazeb (REGN-EB3)	Triple monoclonal-antibody cocktail	Atoltivimab + maftivimab + odesivimab (anti-GP)	FDA 2020	Treatment of EVD caused by EBOV
Ebanga (ansuvimab; mAb114)	Single human monoclonal antibody	Anti-GP ₁ mAb cloned from an EVD survivor	FDA 2020	Treatment of EVD caused by EBOV

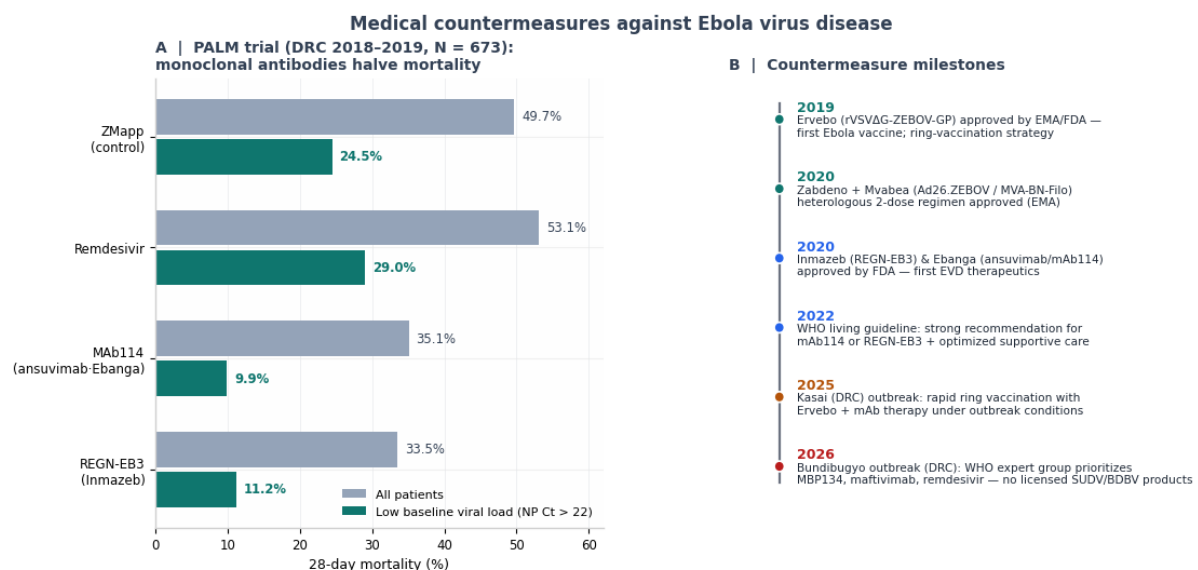


Figure 6. Medical countermeasures against EVD. A. Results of the PALM randomized trial: 28-day mortality by treatment arm, overall and in patients presenting with low baseline viral load (NP cycle threshold > 22). The two monoclonal-antibody arms significantly outperformed ZMapp and remdesivir, with the greatest absolute benefit in early presenters. Data from Ref. [6]. **B.** Milestones in the development and deployment of EVD vaccines and therapeutics, 2019–2026

Viral Persistence and Post-Ebola Sequelae

Clearance of viremia is not the end of the virus–host relationship. EBOV RNA persists in immunologically privileged sites — the testes, the eye, the central nervous system, the placenta and breast milk — for months to years after recovery. Viral RNA has been detected in the semen of a majority of male survivors six to twelve months after illness, with occasional persistence well beyond a year, and sexual transmission from survivors has been documented.^[43] Most dramatically, genomic epidemiology traced the 2021 Guinean outbreak to viral persistence and reactivation in a survivor of the 2013–2016 epidemic — evidence that EBOV can smolder in a single host for at least five years before reigniting transmission.^[46] Survivors commonly carry a burden of "post-Ebola syndrome": uveitis (sometimes with virus detectable in ocular fluid), arthralgia and musculoskeletal pain, neurological and cognitive deficits, and hearing loss, documented in longitudinal cohorts in Liberia and Uganda.^{[44], [45]} These observations make long-term clinical follow-up, semen testing and survivor-centered care integral parts of outbreak control — and raise the unresolved immunological question of how the virus

negotiates survival in sites where antibody and T-cell surveillance are attenuated.

Conclusions and Future Directions

Half a century after its discovery, Ebola virus is no longer an untreatable enigma. Its molecular strategy is now understood in unusual depth: a compact genome whose seven proteins replicate with industrial efficiency while VP35 and VP24 dismantle the interferon system and the glycoprotein deceives humoral immunity. The resulting disease is an immunological race — and the last decade has shown that the race can be tilted decisively by delivering GP-specific immunity from the outside, whether prophylactically (rVSV- and adenovirus-vectored vaccines deployed by ring vaccination) or therapeutically (potent monoclonal antibodies given early). The PALM trial stands as a landmark not only of therapeutics but of immunology translated into survival.^[6]

The agenda ahead is clear. Countermeasures must be extended beyond *Zaire ebolavirus* to Sudan, Bundibugyo and Tai Forest viruses — a need made urgent by the outbreaks of 2025–2026.^{[7], [8]} Host-directed therapies that damp the cytokine storm without crippling viral clearance, biomarker-guided triage to concentrate antibody therapy on those who benefit most, post-exposure prophylaxis for high-risk contacts, and a mechanistic understanding of persistence in survivors are all active frontiers. And beneath them all lies the ecological question with which EVD always begins: how a bat-borne virus crosses into humans. The molecular and immune responses that determine the fate of an infected patient are, in the end, the fine structure of a much larger ecological encounter.

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