Review Article

Hemorrhagic Fever Viruses: Epidemiology, Pathogenesis and Emerging Control Strategies

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Abstract | Hemorrhagic fever diseases (HFDs) are severe viral illnesses caused by pathogens from 4 main families, mainly *Filoviridae*, *Arenaviridae*, *Flaviviridae*, and *Bunyaviridae*. These diseases are characterized by high fever, vascular leakage, and multi-organ dysfunction, with case fatality rates reaching 90 % in untreated cases. Transmission occurs through zoonotic spillover from animal reservoirs (*i.e.*, bats, rodents, and arthropods) and human-to-human contact. Recent advances include the rVSV-ZEBOV Ebola vaccine and monoclonal antibody therapies, yet most HFDs lack specific treatments. Key challenges persist in diagnostics, outbreak containment, and climate-driven geographic expansion of vectors. The aim of this review is to improve current knowledge on HFD pathogenesis, epidemiology, and control strategies, highlighting critical gaps in global preparedness. Strengthening surveillance systems, developing pan-HFD countermeasures, and implementing One Health approaches are essential for mitigating these lethal viral pathogens.

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Introduction

Hemorrhagic fever diseases are zoonotic infections that pose significant common health threats due to their high mortality levels and potential for epidemic spread. Notable examples include Ebola virus disease (EVD), Lassa fever, Crimean-Congo hemorrhagic fever (CCHF), Marburg virus disease (MVD), yellow fever, and Dengue hemorrhagic fever (DHF). These diseases are endemic in tropical or subtropical regions, besides sporadic outbreaks causing global concern (WHO, 2023). HFDs include a group of severe and fatal viral illnesses characterized *via* high fever, bleeding diathesis, and multi-organ failure. These diseases are caused by several distinct families of RNA viruses, including *Filoviridae* (Ebola and Marburg viruses), *Arenaviridae* (Lassa with Junin viruses), *Flaviviridae* (dengue and yellow fever viruses), and *Bunyaviridae* (Crimean-Congo hemorrhagic fever and Rift Valley fever viruses). Clinical manifestations of HFDs range from mild febrile illness to severe hemorrhagic syndromes with

case fatality rates of more than 90 % in some outbreaks (Feldmann *et al.*, 2020). The objective of this study is to display the epidemiology, pathogenesis, and merging control strategies of HFDs.

Epidemiology of hemorrhagic fever diseases

The epidemiology of HFDs is strongly linked to associated zoonotic origins, with natural reservoirs including bats, mosquitoes, rodents, or ticks. Most of these viruses circulate calmly in animal populations, occasionally transmitted to human being *via* direct contact with infected animals, contaminated environments, and/ or insect vectors (Peters *et al.*, 2022). HFDs include several types including Ebola and Marburg viruses that are primarily found in Central and West Africa (Feldmann *et al.*, 2020), Lassa fever that is endemic in West Africa, particularly Nigeria, Sierra Leone, and Liberia (Richmond and Baglole, 2023). Crimean-Congo hemorrhagic fever that is prevalent in Africa, the Middle East, Eastern Europe, and Asia (Ergonul and Whitehouse, 2021). Dengue hemorrhagic fever that is widespread in Southeast Asia, Latin America, and the Pacific (Bhatt *et al.*, 2022).

Once introduced into human populations, some HFDs such as Ebola, Marburg, and Lassa can spread rapidly through person-to-person transmission, particularly in settings with poor infection control measures, such as healthcare facilities and densely populated urban areas (WHO, 2023). Epidemiology of HFDs is presented in Table 1.

Transmission dynamics of hemorrhagic fever viruses

The transmission dynamics of HFVs are governed by complex interactions among zoonotic reservoirs, vectors, human behaviors, and environmental factors, creating distinct epidemiological patterns for each pathogen. Primary zoonotic transmission occurs through diverse routes, such as direct contact with infected animals (e.g., Ebola *via* bushmeat handling and Lassa fever through Mastomys rodent excreta), arthropod vectors (Aedes mosquitoes for dengue andticks for CCHF), or aerosolized rodent secretions (arenaviruses in agricultural settings) (Peters *et al.*, 2022). Human-to-human transmission mechanisms vary significantly by virus, with filoviruses (Ebola, Marburg) spreading efficiently through direct contact with bodily fluids (case reproduction number R0 = 1.5-2.5 in outbreaks), while arenaviruses such as Lassa exhibit more limited secondary transmission (R0 < 1), except in nosocomial settings (WHO, 2023). Superspreading events disproportionately drive epidemics, as demonstrated by the 2014-2016 Ebola outbreak where 3 % of cases generated 61 % of transmissions (Lloyd-Smith *et al.*, 2021), often linked to funeral practices or healthcare exposures. Environmental persistence of viruses (e.g., Ebola in semen for >500 d, CCHF in tick eggs trans-ovarially) enables intermittent resurgence (Deen *et al.*, 2022). Emerging data reveal climate-sensitive transmission patterns, with expanding geographic ranges for Aedes-borne diseases (*i.e.*, dengue and yellow fever) and CCHF in warming temperate zones (Messina *et al.*, 2022). The convergence of urbanization,

Table 1: *Epidemiology of hemorrhagic fever diseases.*

Disease	Country/Region	Key findings	Reference
Ebola Virus Disease (EVD)	West Africa, Guinea, Liberia, and Sierra Leone.	2014–2016 outbreak caused > 28,000 cases, case fatality rate (CFR) ~40–70 %, zoonotic spillover from bats.	WHO (2016)
Marburg Virus Disease (MVD)	Uganda and Angola.	Outbreaks in 2005 (Angola, CFR ~90%) and 2017 (Uganda), fruit bats identified as reservoirs.	Amman *et al.* (2020)
Lassa Fever	Nigeria and West Africa.	Annual outbreaks with increasing cases, CFR ~15–20 %; rodent-to-human transmission predominant.	Richmond and Baglole (2023)
Crimean-Congo Hemorrhagic Fever (CCHF)	Turkey, Iran, and Pakistan.	Tick-borne transmission, nosocomial outbreaks reported, CFR ~10–40 %.	Ergonul and Whitehouse (2021)
Dengue Hemorrhagic Fever (DHF)	Southeast Asia and Latin America.	Aedes mosquitoes as vectors, severe dengue linked to secondary infections, CFR ~1–5 %.	Bhatt *et al.* (2022)
Yellow Fever	Brazil and Africa.	Resurgence in Brazil (2016–2018); mosquito-borne; CFR ~20–50 % in severe cases.	WHO (2023)
Rift Valley Fever (RVF)	Kenya and Saudi Arabia.	Outbreaks linked to livestock; mosquito vectors, CFR ~1 % (severe cases ~50 %).	Peters *et al.* (2022)
Hantavirus Hemorrhagic Fever	South Korea, and Americas.	Rodent-borne; Hantaan virus (Asia) and Sin Nombre virus (Americas), CFR varies (5–15 %).	Jonsson *et al.* (2021)

Table 2: *Organ-specific damage in hemorrhagic fever diseases.*

Organ system	Key pathological findings	Associated viruses	Clinical manifestations	References
Liver	Midzonal necrosis, hepatocyte apoptosis, and Councilman bodies.	Yellow fever, Crimean-congo hemorrhagic fever (CCHF), and Ebola.	Jaundice, elevated transaminases (AST>ALT), and coagulopathy	Paessler and Walker (2022)
Kidneys	Acute tubular necrosis, and interstitial hemorrhage.	Hantaviruses, Lassa, and CCHF.	Oliguric renal failure, proteinuria, and hematuria	Gupta *et al.* (2021)
Lungs	Pulmonary edema, alveolar hemorrhage, and hyaline membranes.	Hantaviruses, and severe dengue.	ARDS, hypoxemia, and respiratory failure	Schieffelin *et al.* (2020)
Heart	Myocarditis, and subendocardial hemorrhage.	Lassa, yellow fever, and Marburg.	Cardiogenic shock, arrhythmias, and troponin elevation	Younan *et al.* (2022)
CNS	Perivascular cuffing, microglial nodules, and neuronal apoptosis.	Ebola, Marburg, and Lassa.	Encephalopathy, seizures, and coma	McElroy *et al.* (2019)
Spleen/ Lymphoid	Lymphocyte depletion, necrosis, and hemophagocytosis.	All Viral hemorrhagic fevers (VHFs) (especially Ebola).	Immunosuppression, and secondary infections	Feldmann *et al.* (2020)
Gastrointestinal tract	Mucosal hemorrhage, and ischemic enteritis.	Ebola, Marburg, and CCHF.	Hematemesis, melena, and diarrhea	WHO (2023)

land-use changes, and global travel has amplified spillover risks, necessitating integrated surveillance at human-animal-environment interfaces to predict and prevent outbreaks.

Pathogenesis

Hemorrhagic fever diseases (HFDs) are caused by diverse RNA viruses that induce severe systemic infections, leading to vascular dysfunction, coagulopathy, and multi-organ failure. The pathogenesis involves complex interactions between viral factors and host immune responses. Target cells of viral entry and initial infection are endothelial cells (primary target in most HFDs, leading to vascular leakage), macrophages and dendritic cells (trigger cytokine storms), liver cells (e.g., in Yellow Fever, causing hepatocyte necrosis), and platelets and megakaryocytes (leading to thrombocytopenia).There are different mechanisms of viralrntry to human that depend on the type of virus that includes Filoviruses (Ebola, Marburg), which use glycoprotein (GP) to bind host receptors (NPC1, TIM-1), Arenaviruses (Lassa) that enter *via* α-dystroglycan and transferrin receptors. Flaviviruses (Dengue, Yellow Fever) that infect *via* DC-SIGN, and other C-type lectin receptors and Bunyaviruses (CCHF, Hantavirus), which attach to integrins and mediate endocytosis (Feldmann *et al.*, 2020; Peters *et al.*, 2022).

Immune system evasion and viral replication in hemorrhagic fever diseases

Hemorrhagic fever viruses employ sophisticated strategies to evade host immune defenses and facilitate robust viral replication, which are central to their pathogenicity. A key mechanism involves the suppression of the interferon (IFN) response; a critical first line of antiviral defense, for instance, Ebola virus VP35 protein directly inhibits RIG-I-like receptor signaling (Basler and Amarasinghe, 2021), while Lassa virus nucleoprotein (NP) disrupts the activation of interferon regulatory factors (IRFs) (Hastie *et al.*, 2017). Additionally, many of these viruses downregulate the major histocompatibility complex class I (MHC-I) molecules on the infected cells, impairing antigen presentation to CD8+ T cells and enabling immune escape (Feldmann *et al.*, 2020). Simultaneously, rapid viral replication occurs in permissive cells such as macrophages, dendritic cells, and endothelial cells, leading to high viral loads that further overwhelm the host immune system (Peters *et al.*, 2022). This unchecked replication triggers excessive cytokine production (e.g., TNF-α, IL-6, and IL-1β) through the activation of inflammasomes and Toll-like receptors, contributing to the characteristic "cytokine storm" observed in severe cases (McElroy *et al.*, 2019). Combination of immune evasion and uncontrolled viral spread establishes a vicious cycle of systemic inflammation, endothelial dysfunction, and tissue damage, ultimately driving disease progression towards hemorrhage, shock, and multi-organ failure (WHO, 2020).

Cytokine storm and systemic inflammation in hemorrhagic fever diseases

The pathogenesis of HFDs is characterized by a dysregulated immune response culminating in a cytokine storm; a hyper-inflammatory state that drives systemic tissue damage and multi-organ failure.

Following viral infection of macrophages and dendritic cells, excessive production of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and interferon-gamma (IFN-γ) occurs *via* the activation of pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs) (McElroy *et al*., 2019). This cytokine surge disrupts endothelial barrier function by upregulating adhesion molecules (e.g., ICAM-1, VCAM-1) and increasing vascular permeability, which facilitates plasma leakage and contributes to hypotensive shock (Feldmann *et al*., 2020). Nowadays, the over activation of NLRP3 inflammasome pathways, particularly the NLRP3 inflammasome, exacerbates IL-1β with IL-18 secretion, and amplifies the inflammatory cascade as reported by Gupta *et al*. (2021). The resulting systemic inflammation is strongly compounded by coagulopathy, as tissue factor (TF) expression above activated monocytes triggers disseminated intravascular coagulation (DIC), leading to widespread microthrombosis with hemorrhagic manifestations (Schieffelin *et al*., 2020). Clinical manifestations associated with this infection, including hemodynamic instability, progressive organ dysfunction, and capillary leak syndrome associated with the severity of secreted cytokines storm correlate directly with the rates of mortality such as in Ebola infections, Lassa fever, and/or severe dengue (WHO, 2020). Modern therapeutic strategies encourage triggering of specific cytokines production (like IL-6 receptor antagonists) with broader immunomodulation (such as corticosteroids) that have shown limited efficacy, underscoring the necessity for precision approaches to mitigate the life-threatening complications of viral infections (van Griensven *et al*., 2022).

Table 3: *Previous studies on the hemorrhagic fever disease.*

Virus	Study focus	Key findings	Country	Year	Reference
Dengue	Pathogenesis	First described antibody-dependent enhancement.	Thailand	1970	Halstead (1970)
Lassa	Treatment	Ribavirin reduces mortality from 55% to 5%	Liberia	1986	McCormick *et al.* (1986)
Lassa	Seroprevalence	15 % sero-positivity in endemic regions	Sierra Leone	1987	McCormick *et al.* (1987)
CCHF	Vector biology	Demonstrated transovarial transmission in ticks.	South Africa	1989	Shepherd *et al.* (1989)
Hantavirus	Syndrome description	First identified hantavirus pulmonary syndrome.	USA	1994	Duchin *et al.* (1994)
Rift Valley	Outbreak investigation	Linked epidemic to heavy rainfall and mosquito vectors.	Kenya	1998	Woods *et al.* (1998)
Ebola	Reservoir identification	Found Ebola virus RNA in fruit bats.	Gabon, Congo	2005	Leroy *et al.* (2005)
Marburg	Animal reservoir	Identified Egyptian fruit bats as natural hosts.	Uganda	2007	Towner *et al.* (2006)
Yellow Fever	Vaccine efficacy	Showed 17D vaccine provides lifelong immunity.	Brazil	2013	Gotuzzo *et al.* (2013)
Ebola	Outbreak dynamics	Characterized transmission chains in West Africa outbreak.	uinea	2015	Faye *et al.* (2015)
Ebola	Vaccine efficacy	rVSV-ZEBOV showed 97.5 % efficacy	Guinea	2016	Henao-Restrepo *et al.* (2021)
Ebola	mAb treatment	REGN-EB3 reduced mortality to 33.5 %.	DRC	2019	Mulangu *et. al.* (2019)
Lassa	Viral persistence	Detected viral RNA in semen for 6 months post-infection.	Nigeria	2020	Whitmer *et al. (*2020)
CCHFV	Virology, pathogenesis, pathology and clinician guidance	Clarified virus-host interactions and clinical presentation, and aids in early diagnosis and management.	USA	2024	Frank *et al.* (2024)
CCHFV	Genetic diversity and reassortment in human isolates	Identified re-assortant strains in Pakistan, and indicating active viral evolution	Pakistan	2024	Umair *et al.* (2024)
CCHFV	Sero-surveillance in domestic ruminants	High seroprevalence in goats and sheep suggests endemicity in southern Spain.	Spain	2024	Baz-Flores *et al.* (2024)
CCHFV	Case report: Immunoglobulin and cytokine response in fatal infection	Severe disease linked to delayed antibody response and uncontrolled cytokine storm.	Senegal	2025	Mhamadi *et al. (*2025)

Endothelial dysfunction and vascular leakage in hemorrhagic fever diseases

The harshness of severe HFDs is attributed to the development of profound dysfunction of endothelium leading to catastrophic vascular leakage, as a pathophysiological process that strongly underlies shock besides multi-organ failure. Moreover, viral infection of endothelium cells can directly disrupt them *via* vascular integrity by multiple mechanisms, including downregulation of the tight junction proteins (like claudin-5, occludin) with adherens junctions (VE-cadherin), leading to an increase in para cellular permeability (Paessler and Walker, 2022). Simultaneously, the cytokine storm characterizing these infections, particularly elevated levels of VEGF, angiopoietin-2, and TNF-α, induces cytoskeletal reorganization in endothelial cells, further compromising barrier functions (Goldsmith *et al.*, 2021). Loss of endothelial integrity is exacerbated by virus-induced apoptosis *via* both intrinsic (mitochondrial) and extrinsic (death receptor) pathways, as demonstrated in Ebola and dengue virus infections (Rasmussen *et al.*, 2023). Additionally, the dysregulated host response leads to widespread activation of the coagulation cascade, with thrombin generation promoting further endothelial activation and platelet consumption (Schieffelin *et al.*, 2023). The resulting clinical manifestations include progressive hemoconcentration, third spacing of fluids, and the characteristic hemorrhagic diathesis observed in severe cases. Importantly, emerging evidence suggests that glycocalyx shedding, the degradation of the protective endothelial surface layer, may serve as both a biomarker of disease severity and a therapeutic target in hemorrhagic fevers (Younan *et al.*, 2022).

Organ-specific damage in hemorrhagic fever diseases

Hemorrhagic fever viruses induce distinct patterns of organ-specific damage that contribute to their high mortality rates, with pathological manifestations varying by viral family and host factors. The liver is frequently targeted, particularly by yellow fever and Crimean-Congo hemorrhagic fever viruses, which cause midzonal necrosis, hepatocyte apoptosis, and councilman bodies, leading to jaundice, coagulopathy, and acute liver failure (Paessler and Walker, 2022). Renal dysfunction; a hallmark of Hantavirus infections, results from direct viral injury to tubular epithelial cells and immune-mediated damage, manifested as acute kidney injury with proteinuria and oliguria (Gupta *et al.*, 2021). Pulmonary involvement predominates in Hantavirus pulmonary syndrome and severe dengue, where cytokine-driven capillary leak syndrome causes noncardiogenic pulmonary edema and acute respiratory distress syndrome (ARDS) (Schieffelin *et al.*, 2020). Cardiac complications, including myocarditis and arrhythmias, are particularly severe in Lassa fever and yellow fever due to direct viral infection of cardiomyocytes and ischemia from hypovolemic shock (Younan *et al.*, 2022). Neurological features result from mild encephalopathy towards fatal encephalitis of late-stage Ebola with Marburg virus infections, where viral penetration of the blood-brain barrier can be triggered and neuroinflammation with neuronal apoptosis occurs (McElroy *et al.*, 2019). The spleen besides lymphoid tissues has shown markedly extensive lymphocyte depletion with necrosis, which contributes to secondary infections and immunosuppression (Feldmann *et al.*, 2020). These organ-specific illnesses collectively drive multi-organ failure of the terminal haemorrhagic fever pathologies, with the pattern of severity regarding injury reflecting both intensity of host immune response and viral tropism (WHO, 2023).

Diagnostic advances

These aforementioned viral diseases can be diagonized *via* molecular techniques (*i.e.*, Reverse transcription polymerase chain reaction (RT-PCR) and antigen detection assays that have improved early diagnosis (Bhatt *et al.*, 2022). RT-PCR is a technique used to detect the RNA, followed by polymerase chain reaction (PCR) amplification, and is widely used in the diagnostic studies due to its high sensitivity and specificity (Al-Rashid, 2023). Antigen detection assays are fast techniques used to detect specific proteins from pathogens, such as viruses, these techniques provide quicker results compared to RT-PCR, but are usually less sensitive (Mahasem, 2021). However, the serological assays remain crucial for surveillance (Ergonul and Whitehouse, 2021), used to detect antibodies in the human blood after infection to confirm whether an individual had been earlier exposed to a microbial pathogen or not (Whitman *et al.*, 2020).

Synthesizing key findings on hemorrhagic fever epidemiology and recent studies

The compiled studies revealed critical patterns in hemorrhagic fever (HF) epidemiology while highlighting both progress and persistent gaps in our understanding of these dangerous pathogens. Several

important themes have emerged.

First, the geographic distribution of HF viruses continues to evolve, with multiple studies confirming expansion beyond traditional endemic zones. The 2015 Ebola outbreak in West Africa (Faye *et al.*, 2015) and subsequent spread to urban areas demonstrated how quickly these viruses can exploit new ecological niches. Similarly, climate-linked hantavirus spread in Argentina (Piudo *et al.*, 2005) underscore how environmental changes are reshaping HF risk maps.

Second, transmission dynamics appear more complex than previously understood. While animal reservoirs remain the primary source as reported by Leroy *et al.* (2005), human-to-human transmission potential varies dramatically among the viruses. Lassa virus persistence findings (Whitmer *et al.*, 2018) identified new challenges in managing sexual transmission risks during post-outbreak periods.

Treatment and prevention advances have been uneven across HF viruses. The rVSV-ZEBOV vaccine success (Henao-Restrepo *et al.*, 2021) and monoclonal antibody breakthroughs (Mulangu *et al.*, 2019) for Ebola contrast sharply with the lack of approved countermeasures for most other HFs. Even where treatments exist, such as ribavirin for Lassa (McCormick *et al.*, 1986), real-world implementation barriers persist in endemic regions.

Treatment and vaccination strategies for hemorrhagic fever diseases

The management of HFDs remains challenging due to the limited availability of the targeted therapies, necessitating a combination of supportive care, antiviral medications, and vaccination where applicable. Supportive therapy forms the cornerstone of treatment, focusing on fluid resuscitation, electrolyte balance, and management of coagulopathy to prevent shock and multi-organ failure (WHO, 2023). For specific viruses, antiviral agents such as ribavirin (effective against Lassa fever and some arenaviruses) and favipiravir (investigated for Ebola and CCHF) have shown variable efficacy, though their use is often limited by toxicity and late-stage administration (Siegel *et al.*, 2022). Immunotherapies, including monoclonal antibodies (e.g., REGN-EB3 with mAb114 for Ebola), have demonstrated significant survival benefits of clinical trials by neutralizing viral particles and modulating immune responses (Mulangu *et al.*, 2019). Vaccination has emerged as a critical preventive approach, and the rVSV-ZEBOV vaccine showed >97 % efficacy towards Ebola ranges as a vaccination good trial (Henao-Restrepo *et al.*, 2021). However, vaccine development for other HFDs, such as Lassa fever and CCHF, remains in experimental stages, hindered by antigenic diversity and limited commercial incentives (Bente *et al.*, 2020). Despite above advances, major challenges persist, including cold-chain in vaccines requirements, late presentation of illnesses, and absence of standardized protocols for emerging viruses. Future strategies must prioritize broad-spectrum antivirals, rapid diagnostics, and universal vaccine platforms to come up with the evolving threat regarding HF in endemic regions (Feldmann *et al.*, 2020).

Public health challenges and control strategies for hemorrhagic fever diseases

Hemorrhagic fever diseases (HFDs) considered as formidable common health challenges because of their epidemic nature of high rate fatality rates and complex methods of transmission, necessitating multifaceted control dynamics. Early detection with surveillance remains the critical obstacle, as initial symptoms usually mimic common febrile illnesses, causing delayed diagnosis besides increased transmission risks, mainly under resource-limited settings where Polymerase Chain Reaction (PCR) capacity is very scarce (WHO, 2023). Healthcare-associated outbreaks can amplify epidemics, such as demonstrated in the 2014-2016 Ebola crisis during inadequate infection prevention besides control (IPC) measures (Schieffelin *et al.*, 2020). Zoonotic spillover prevention requires coordinated One Health approaches to be achieved, including rodent control of Lassa fever and livestock vaccination of Rift Valley fever, (Bente *et al.*, 2020). Community engagement poses another challenge, such as cultural burial practices, necessitating culturally sensitive risks in communication strategies (Fallah *et al.*, 2022).Vaccination campaigns, while being successful towards Ebola *via* ring vaccination, to face logistical barriers in remote areas that remain unavailable for most HFDs (Henao-Restrepo *et al.*, 2021). Climate change besides urbanization is expanding vector habitats mainly in rural areas, increasing arboviral HFDs outbreaks such as dengue besides yellow fever, necessitating adaptive vector programs and control (Gubler, 2022). Effective control gathering with strengthening health systems through laboratory

networks and rapid response teams besides cross-border collaboration can be as outlined in the WHO's Global network for preventing HFD (WHO, 2023). Sustainable solutions should integrate surveillance innovations such as AI-powered outbreak prediction, thermostable vaccines, and community-led interventions as an obvious address of evolving common threats.

Conclusions and Recommendations

Hemorrhagic fever diseases pose an ongoing global health threat due to their severe clinical manifestations, epidemic potential, and complex transmission dynamics. While recent advances in vaccines and therapeutics have improved outbreak response capabilities, significant gaps remain in prevention and treatment for many pathogens. Effective control requires strengthened surveillance systems, accelerated research into broad-spectrum countermeasures, and robust public health infrastructure, particularly in endemic regions. Addressing the interconnected challenges of zoonotic spillover, climate change impacts, and health system vulnerabilities will be critical for future pandemic preparedness. Sustained international cooperation and investment are essential to mitigate the substantial morbidity and mortality caused by these deadly viral pathogens. This study recommends immediate implementation of strict infection control measures if the microbial infection occurs and highlights the importance of public health interventions, such as contact tracing, separation, and community awareness, particularly during epidemics. Finally, it underscores the essential of continuing research studies on vaccines and targeted therapies.

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Novelty Statement

This review presents recent advances in understanding immune responses to viral infections, highlights unresolved issues, and suggests future research pathways.

Author's Contribution

Eman A. Muhsin: Conceptualization and formal analysis.
Eman A. Muhsin, Shahrazad Ahmed Khalaf and Riyadh Hameed Nsaif: Investigation.
Shahrazad Ahmed Khalaf and Riyadh Hameed Nsaif: Data curation and writing original drafts.
Shahrazad Ahmed Khalaf: Reviewing, editing the manuscript, and scientific corrections.

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