IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

# Immune Storms And Strategic Shields: A Multidisciplinary Lens on Viral Haemorrhagic Fevers

**[1] S. Vedhasree, [2] B. Gopika,[3] B.Bharathi*, [4] Deepa C.Philip**

[1],[2] BSc Physician Assistant 3rd year, MMM College of Health Sciences, Chennai
[3]Associate Professor, Microbiology, MMM College of Health Sciences, Chennai
[4]Principal, MMM College of Health Sciences, Chennai

**Abstract**: Viral Haemorrhagic Fevers (VHFs) remain a significant public health challenge, especially in regions with limited healthcare resources. These diseases, caused by diverse RNA viruses such as Arenaviruses, Filoviruses, and Bunyaviruses, share clinical features like fever, bleeding, and multiorgan dysfunction, often driven by uncontrolled immune responses. The absence of widely effective vaccines and the complexity of treatment underline the need for early detection and supportive care. Recent experimental models have highlighted cytokine storms as critical determinants of disease severity, offering new avenues for immunomodulatory therapy. Globally, efforts to improve outbreak readiness emphasize community engagement, rapid diagnostics, and cross-border collaboration. Environmental and socioeconomic factors increasingly influence outbreak patterns. Therefore, the development of accessible vaccines, antivirals, and innovative fluid management strategies is imperative for future control.

Key words: VHFs, cytokine storm, immunopathogenesis, viral outbreaks, hemorrhagic fever, antiviral therapy

## 1. Classification and Clinical Features of VHFs

Viral haemorrhagic fevers are caused by enveloped RNA viruses belonging to several families—Arenaviridae, Filoviridae, Bunyaviridae, and Flaviviridae. These viruses are zoonotic, transmitted via arthropod vectors or direct contact with infected animal excreta or bodily fluids. Lassa and Lujo viruses, endemic to Africa, often originate from rodent exposure. Lassa virus typically leads to mild illness but may progress to severe disease in hospitalized cases, with symptoms like fever, hypotension, and CNS involvement developing within 7–10 days (Department of Health, South Africa, 2014; Ftika and Maltezou, 2013; Fhogartaigh and Aarons, 2015; Ignatyev *et al*., 1996; Demby *et al*., 1994; Frolov *et al*., 1997). Lujo virus presents similarly, although bleeding is minimal (Department of Health, South Africa, 2014; Ftika and Maltezou, 2013). Ribavirin remains a key treatment option, albeit with variable availability and efficacy (Department of Health, South Africa, 2014).

Among Bunyaviruses, Crimean-Congo haemorrhagic fever (CCHF) and Rift Valley fever (RVF) are notable. CCHF is usually acquired through tick bites or handling infected animals, with a mortality rate of up to 50%. Symptoms escalate from fever and headache to widespread bleeding by day four. Predictors of poor prognosis include low platelet counts and elevated AST levels (Department of Health, South Africa, 2014; Ftika and Maltezou, 2013; Ericsson *et al*., 2001; Fhogartaigh and Aarons, 2015; Demby *et al*., 1994; Ignatyev *et al*., 1991). RVF, while usually mild, may rarely cause severe complications such as encephalitis, hemorrhage, or vision loss (Department of Health, South Africa, 2014; Ftika and Maltezou, 2013; Fhogartaigh and Aarons, 2015; Ignatyev *et al*., 1996; Demby *et al*., 1994).

Filoviruses such as Ebola and Marburg viruses are associated with severe outbreaks. These are transmitted through contact with infected body fluids and are known for high mortality. Disease progression involves an initial febrile phase, gastrointestinal distress, and in advanced cases, severe bleeding and shock. The incubation period ranges from 2 to 21 days (Department of Health, South Africa, 2014; Ftika and Maltezou, 2013; Ericsson *et al*., 2001; Ignatyev *et al*., 1996). Early isolation and protective measures are crucial in preventing spread.

**2. Viral hemorrhagic fever Immunopathogenesis and Cytokine Storms**

The hallmark of VHFs is an overactive immune response, especially marked by excessive cytokine release. Studies in animal models reveal that elevated levels of TNF-α, IL-6, IL-1β, and IFN-γ are closely linked to disease severity (Fhogartaigh and Aarons,2015; Matua *et al*., 2015 ; Ignatyev *et al*., 1996 ; Demby *et al*., 1994 ; Frolov *et al*., 1997 ; Ignatyev *et al*., 1994 ; Kolokoltsova *et al*., 2010 ; Fritz *et al*., 2008 ; mohamadzadeh *et al*., 2006 ; Rubins *et al*., 2007 ; Wauquier *et al*., 2010 ; Warfield *et al*., 2009 ; Villinger *et al*., 1999 ; Johnson *et al*., 2011). In Ebola and Marburg infections, a combination of suppressed adaptive immunity and heightened pro-inflammatory cytokines leads to vascular leakage and organ failure (Wauquier *et al*., 2010 ; Hutchinson *et al*., 2001 ; Warfield *et al*., 2009).

Clinical data from Turkey in CCHF cases have shown that elevated IL-6 and TNF-α levels correlate with severity and coagulation abnormalities, while IL-10 appears protective (Ftika and maltezou, 2013 ; Bozza *et al*., 2008). Similar findings in Dengue and Arenavirus infections support the central role of cytokine dysregulation (Dejean *et al*., 1987 ;Mahanty *et al*., 2001 ; Schmitz *et al*., 2002 ;Poljkov *et al*., 1975 ; Bente *et al*., 2010 ; Shresta *et al*., 2006 ; Connolly *et al*., 1999 ; Johnson *et al*., 2011) . Genetic factors may further influence host susceptibility (Demby *et al*., 1994 ; Frolov *et al*., 1997 ; Ignatyev *et al*., 1991).

**3. Experimental Models and Immunotherapeutics**

High-containment studies in guinea pigs and mice have examined treatments like recombinant IL-1 receptor antagonists and anti-TNF-α antiserum. These interventions lowered cytokine levels and improved survival in Lassa and Marburg virus infections (Ignatyev *et al*., 1991, 1994, 1996c).

Results demonstrated that cytokine storms, not just viral replication, contribute significantly to mortality. Blocking TNF-α or modulating IL-1 responses offers therapeutic potential. Continued research in animal models is vital, given the ethical challenges of human trials.

**4. Global Response Strategies and Outbreak Preparedness**

Analyses of past outbreaks (e.g., 2014–2016 Ebola) emphasize the importance of early detection, isolation, community involvement, and coordinated global action. Countries with decentralized surveillance and inter-agency cooperation managed outbreaks more effectively.

WHO's International Health Regulations and CDC guidelines offer strategic frameworks but often require regional adaptation. Key recurring challenges include limited laboratory capacity, undertrained personnel, and inconsistent funding (2000–2023 reviews).

**5. Advances in Diagnosis and Therapy**

RT-PCR remains the gold standard for diagnosis. Newer methods such as multiplex PCR, CRISPR-based platforms, and point-of-care tests are under development (Feldmann and Geisbert, 2011; Das *et al*., 2015; Humaidi *et al*., 2021). Treatment strategies are stage-specific: antivirals like ribavirin are useful early; immunomodulators are used in coagulopathy phases (Ippolito *et al*., 2012; Ergonul *et al*., 2007).

Monoclonal antibodies such as Inmazeb and Ebanga have improved outcomes in Ebola (Mulangu *et al*., 2019; FDA, 2020). Meanwhile, fluid therapy protocols, including remote-controlled IV systems, offer scalable care solutions during high-risk outbreaks (Jacob *et al*., 2016).

**6. Vaccines, Therapeutics, and Future Public Health Priorities**

Several vaccines (e.g., ERVEBO for Ebola) and therapeutics (e.g., favipiravir, remdesivir) show promise (WHO, 2022a; Gowen *et al*., 2007). Host-targeted therapies such as SAHH inhibitors and monoclonal antibodies are under exploration. However, challenges like affordability, infrastructure, and equitable access persist.

VHFs are exacerbated by environmental disruptions and weak health systems. Enhanced surveillance, international collaboration, and community-based preparedness will be essential for mitigating future outbreaks. Strategic stockpiling, flexible clinical models, and sustained research funding must continue to drive innovation and resilience.

**7.Mechanisms of Vascular and Immune System Disruption**

VHFs cause extensive vascular damage by targeting endothelial cells, leading to capillary leak, edema, and hypotension. One central mechanism involves the disruption of endothelial tight junctions due to high levels of pro-inflammatory cytokines like TNF-α and IL-6. This results in compromised vascular integrity, contributing to shock and multiorgan failure (Marty *et al*., 2006; Russier *et al*., 2014).

Infected macrophages and dendritic cells act as primary viral targets but fail to launch a productive immune defense. Instead, these cells become viral factories, releasing massive quantities of cytokines, chemokines, and reactive oxygen species. This immune misfiring weakens the adaptive response and promotes viral dissemination. Viruses like Ebola and Lassa actively suppress type I interferon responses by blocking pathways such as RIG-I and STAT1, aiding immune evasion (Baize *et al*., 2004; Kang *et al*., 2021).

In severe cases, T-cell apoptosis occurs via the Fas/FasL and TRAIL pathways, undermining cell-mediated immunity. Additionally, overexpression of inhibitory molecules like PD-1 and CTLA-4 contributes to T-cell exhaustion (Wauquier *et al*., 2010; Zhu *et al*., 2009). These combined factors promote immunopathology rather than viral clearance.

**8.Organ-Specific Complications and Disease Progression**

While all VHFs involve systemic inflammation, individual organs are affected in distinct ways. The liver often shows elevated transaminases (ALT, AST), reflecting hepatocellular injury. Renal damage may lead to oliguria and metabolic imbalance. Hemorrhagic manifestations such as petechiae, epistaxis, and internal bleeding stem from platelet dysfunction and DIC (disseminated intravascular coagulation) (Mariappan *et al*., 2021).

Autopsy reports have identified viral presence in multiple organs—including the spleen, lungs, brain, and even reproductive tissues—indicating systemic spread. In some cases of Junín virus, survivors exhibit neurological complications due to direct viral invasion of the CNS (Paessler and Walker, 2013).

Ebola virus glycoproteins, even in the absence of active viral replication, can independently trigger endothelial damage by activating inflammatory pathways in vascular tissues. This ability to disrupt host physiology without replication is a major factor contributing to the virus's lethality (Geisbert *et al*., 2003; Moni *et al*., 2022).

**9.Innovations in Therapeutic Strategies**

Modern therapeutic efforts now recognize that managing the host's immune response is as critical as targeting the virus itself. COX-2 inhibitors, CCR2 blockers, and platelet-activating factor antagonists are being studied to dampen inflammation and preserve vascular stability. Natural compounds like caffeic acid conjugates have shown potential in reducing both viral replication and cytokine toxicity (Mohamadzadeh *et al*., 2006).

Treatment timing is vital: early-phase interventions may benefit from immune stimulation (e.g., IFN-β), whereas late-phase care focuses on dampening cytokine overdrive. This dual strategy—immune modulation plus antiviral action—could reduce mortality more effectively than either approach alone (Wauquier *et al*., 2010).

Monoclonal antibody therapies such as Inmazeb (REGN-EB3) and Ebanga (Ansuvimab) are now FDA-approved for Ebola treatment, with evidence showing improved survival when administered early (Mulangu *et al*., 2019). For Lassa and CCHF, research into neutralizing antibodies and post-exposure prophylaxis is ongoing.

**10.Broader Preparedness, Ecological Considerations, and Equity**

Environmental changes are accelerating the spread of VHFs. Urbanization, deforestation, and climate-driven migration of animal vectors (e.g., mosquitoes, rodents, ticks) have led to outbreaks in new regions. Yellow fever, once geographically limited, has reemerged due to the spread of Aedes albopictus, while migratory birds are contributing to the expansion of CCHF (Brady and Hay, 2020; Al-Abri *et al*., 2017).

Unfortunately, many regions most at risk lack the necessary biosafety infrastructure or trained personnel to detect and respond to outbreaks. International collaboration remains essential, but so does regional investment in diagnostic labs, cold chain logistics, and public health education (Fernandez-García *et al*., 2014).

Efforts by CEPI, BARDA, and the WHO aim to fund flexible vaccine platforms such as mRNA and vector-based models that can be rapidly adapted to emerging threats. However, ensuring affordability, accessibility, and cultural acceptance of these tools remains a significant challenge.

**11.Diagnostic Challenges and Technological Advances**

Diagnosis of VHFs is complicated by nonspecific symptoms that overlap with malaria, typhoid, or sepsis. Clinical suspicion alone is often insufficient, particularly in early stages. Serological testing, while useful in convalescent phases, is unreliable during acute infection due to delayed antibody response. Therefore, molecular techniques such as RT-PCR have become the diagnostic gold standard (Feldmann and Geisbert, 2011; Racsa *et al*., 2016).

Novel approaches under development include isothermal nucleic acid amplification (like LAMP), lateral flow assays, and CRISPR-Cas platforms, which aim to deliver rapid and accurate detection even in field settings. Efforts are also underway to enable non-invasive testing using saliva or urine, which could drastically improve sample safety and patient compliance (Das *et al*., 2015; Barnes *et al*., 2020; Humaidi *et al*., 2021).

Despite these innovations, many

regions still lack laboratory capacity and biosafety protocols required for high-risk pathogen testing. Strengthening diagnostic infrastructure in endemic areas remains a top priority.

**12.Host-Virus Interaction and Immune Suppression**

VHF viruses have evolved sophisticated strategies to evade the host immune system. For example, Lassa virus uses its nucleoprotein to degrade viral RNA and block interferon activation, while Ebola employs VP24 and VP35 proteins to suppress STAT1 signaling and hinder dendritic cell maturation (Pythoud *et al*., 2012; Basler *et al*., 2003; Rodrigo *et al*., 2012).

These interactions not only impair initial immune recognition but also dampen T-cell and NK cell activation, creating an immune "blind spot" during early infection. By the time the immune system mounts a response, the virus has often already spread systemically. This delayed response contributes to the hyperinflammatory state observed in late-stage disease (Jin *et al*., 2010; Sung *et al*., 2012).

Furthermore, endothelial cells exposed to viral proteins undergo apoptosis and lose junctional integrity, further exacerbating vascular leak and hypotension. These insights into molecular pathogenesis are driving the development of targeted therapies that restore immune balance without suppressing host defenses.

**13.Strategic Models for Low-Resource Settings**

Given the logistical challenges during outbreaks, especially in regions with limited healthcare personnel, new care delivery models are being explored. One promising approach involves **pulse pressure–guided fluid therapy** using remote-controlled IV systems. This allows clinicians to adjust fluid administration based on non-invasive blood pressure monitoring, reducing the need for constant bedside care and minimizing exposure risk (Jacob *et al*., 2016).

This model has been tested in simulations with promising results and could be adapted for future outbreaks involving viruses like Lassa, Ebola, and Marburg, which are associated with significant fluid loss. The design is simple, cost-effective, and compatible with outbreak conditions in low-income countries.

Combined with mobile diagnostic labs, real-time surveillance tools, and portable isolation units, these innovations represent scalable strategies for frontline outbreak response.

**Conclusion and Recommendations**

Viral haemorrhagic fevers (VHFs) represent a persistent and evolving threat to global health security. Despite advances in molecular diagnostics, immunotherapy, and vaccine development, major gaps remain in detection, response, and equitable access to care. The ability of these viruses to subvert host immunity, combined with ecological changes and weak health infrastructure in many endemic regions, continues to challenge outbreak control efforts.

Future strategies must be grounded in a multidisciplinary framework—integrating clinical care, molecular science, public health, and community engagement. Research should prioritize not only the development of novel antivirals and vaccines but also low-tech solutions such as remote monitoring systems and mobile labs tailored for resource-limited settings.

Key recommendations include:

- **Strengthening diagnostic capacity** in endemic regions through decentralized PCR testing, point-of-care tools, and training programs.
- **Investing in broad-spectrum antiviral development** with support from global public–private partnerships like CEPI and BARDA.
- **Scaling up vaccine trials** for Marburg, Lassa, and CCHF viruses using flexible platforms like mRNA and viral vectors.
- **Implementing real-time surveillance systems** to monitor viral evolution and detect early outbreak signals.
- **Promoting community-level education and risk communication** to encourage early care-seeking and reduce stigma.

Ultimately, controlling VHFs requires more than reactive emergency response—it demands proactive investment in resilient healthcare systems, transparent global cooperation, and sustained political will. With a strategic shift from containment to prevention, the burden of VHFs can be significantly reduced, especially for the world's most vulnerable populations.

## REFERENCES


1. Centers for Disease Control and Prevention. 2020. Viral Haemorrhagic Fevers [homepage on the Internet]. Available from: https://www.cdc.gov/vhf/index.html
2. Department of Health, South Africa. 2014. National guidelines for recognition and management of viral haemorrhagic fevers [homepage on the Internet]. Available from: https://www.medbox.org/national-guidelines-for-recognition-and-management-of-viral-haemorraghic-fevers/download.pdf
3. Ftika, L. and Maltezou, H.C. 2013. Viral haemorrhagic fevers in healthcare settings. *Journal of Hospital Infection*, 83(3): 185–192. https://doi.org/10.1016/j.jhin.2012.10.013
4. Richards, G.A., Weyer, J. and Blumberg, L.H. 2015. Viral haemorrhagic fevers in South Africa. *South African Medical Journal*, 105(9): 748–751. https://doi.org/10.7196/SAMJNEW.8330
5. Ericsson, C.D., Steffen, R. and Isaäcson, M. 2001. Viral Hemorrhagic fever hazards for travelers in Africa. *Clinical Infectious Diseases*, 33(10): 1707–1712. https://doi.org/10.1086/322620
6. Francesco, D., Giulia, C. and Giulia, G. 2016. Contemporary infectious exanthems: An update. *Future Microbiology*, 12(2): 1–23. https://doi.org/10.2217/fmb-2016-0147
7. Fhogartaigh, C.N. and Aarons, E. 2015. Viral Haemorrhagic fever. *Clinical Medicine*, 15(1): 16. https://doi.org/10.7861/clinmedicine.15-1-61
8. Matua, G.A., Van der Wal, D.M. and Locsin, R.C. 2015. Ebola hemorrhagic fever outbreaks: Strategies for effective epidemic management, containment and control. *Brazilian Journal of Infectious Diseases*, 19(3): 308–313. https://doi.org/10.1016/j.bjid.2015.02.004
9. Ignatyev, G.M., Agafonov, A.P., Streltsova, M.A. and Kashentseva, E.A. 1996. Inactivated Marburg virus elicits a nonprotective immune response in Rhesus monkeys. *Journal of Biotechnology*, 44: 111–118.
10. Demby, A.H., Chamberlain, J., Brown, D.W.G. and Clegg, C.S. 1994. Early diagnosis of Lassa fever by reverse transcription-PCR. *Journal of Clinical Microbiology*, 32: 2898–2903.
11. Frolov, A.S., Pika, I.S. and Eroshkin, A.M. 1997. ProMSED: protein multiple sequence editor for Windows 3.11/95. *CABIOS*, 13: 243–248.
12. Ignatyev, G.M., Agafonov, A.P., Streltsova, M.A., Spirin, G.A., Mainagarova, G.I. and Chernii, N.B. 1991. Comparative analysis of some immunological parameters of inactivated Marburg viruses in guinea pigs. *Voprosy Virusologii*, 36: 421–423.
13. Ignatyev, G.M., Streltsova, M.A., Agafonov, A.P. et al. 1994. Immunologic characteristics of guinea pigs with Marburg hemorrhagic fever. *Voprosy Virusologii*, 39: 160–171 (in Russian).
14. Ignatyev, G.M., Streltsova, M.A., Agafonov, A.P., Kashentseva, E.A. and Prozorovsky, N.S. 1996. Experimental study of therapy of Marburg hemorrhagic fever with desferal, ribavirin and homologous interferon. *Voprosy Virusologii*, 41: 206–209.
15. Poljkov, I.V. and Sokolova, N.S. 1975. *Practice of Medical Statistics*. Medicina Press, Leningrad.
16. Bente, D.A., Alimonti, J.B., Shieh, W.-J. et al. 2010. Pathogenesis and immune response of Crimean–Congo hemorrhagic fever virus in a STAT-1 knockout mouse model. *Journal of Virology*, 84(21): 11089–11100.
17. Kolokoltsova, O.A., Yun, N.E., Poussard, A.L. et al. 2010. Mice lacking alpha/beta and gamma interferon receptors are susceptible to Junin virus infection. *Journal of Virology*, 84(24): 13063–13067.
18. Lever, M.S., Piercy, T.J., Steward, J.A. et al. 2012. Lethality and pathogenesis of airborne infection with filoviruses in A129 α/β-/- interferon receptor-deficient mice. *Journal of Medical Microbiology*, 61(Pt 1): 8–15.
19. Shresta, S., Sharar, K.L., Prigozhin, D.M., Beatty, P.R. and Harris, E. 2006. Murine model for dengue virus-induced lethal disease with increased vascular permeability. *Journal of Virology*, 80(20): 10208–10217.
20. Bray, M., Davis, K., Geisbert, T., Schmaljohn, C. and Huggins, J. 1999. A mouse model for evaluation of prophylaxis and therapy of Ebola hemorrhagic fever. *Journal of Infectious Diseases*, 179(Suppl. 1): S248–S258.
21. Connolly, B.M., Steele, K.E., Davis, K.J. et al. 1999. Pathogenesis of experimental Ebola virus infection in guinea pigs. *Journal of Infectious Diseases*, 179(Suppl. 1): S203–S217.

22. Johnson, R.F., Dodd, L.E., Yellayi, S. et al. 2011. Simian hemorrhagic fever virus infection of rhesus macaques as a model of viral hemorrhagic fever: clinical characterization and risk factors for severe disease. *Virology*, 421(2): 129–140.
23. Fritz, E.A., Geisbert, J.B., Geisbert, T.W., Hensley, L.E. and Reed, D.S. 2008. Cellular immune response to Marburg virus infection in cynomolgus macaques. *Viral Immunology*, 21(3): 355–363.
24. Mohamadzadeh, M., Chen, L., Olinger, G.G., Pratt, W.D. and Schmaljohn, A.L. 2006. Filoviruses and the balance of innate, adaptive, and inflammatory responses. *Viral Immunology*, 19(4): 602–612.
25. Rubins, K.H., Hensley, L.E., Wahl-Jensen, V. et al. 2007. The temporal program of peripheral blood gene expression in the response of nonhuman primates to Ebola hemorrhagic fever. *Genome Biology*, 8(8): R174.
26. Wauquier, N., Becquart, P., Padilla, C., Baize, S. and Leroy, E.M. 2010. Human fatal Zaire Ebola virus infection is associated with an aberrant innate immunity and with massive lymphocyte apoptosis. *PLoS Neglected Tropical Diseases*, 4(10): e837.
27. Hutchinson, K.L., Villinger, F., Miranda, M.E., Ksiazek, T.G., Peters, C.J. and Rollin, P.E. 2001. Multiplex analysis of cytokines in the blood of cynomolgus macaques naturally infected with Ebola virus (Reston serotype). *Journal of Medical Virology*, 65(3): 561–566.
28. Bradfute, S.B., Warfield, K.L. and Bray, M. 2012. Mouse models for filovirus infections. *Viruses*, 4(9): 1477–1508.
29. Warfield, K.L., Bradfute, S.B., Wells, J. et al. 2009. Development and characterization of a mouse model for Marburg hemorrhagic fever. *Journal of Virology*, 83(13): 6404–6415.
30. Villinger, F., Rollin, P.E., Brar, S.S. et al. 1999. Markedly elevated levels of interferon (IFN)-gamma, IFN-alpha, interleukin (IL)-2, IL-10, and tumor necrosis factor-alpha associated with fatal Ebola virus infection. *Journal of Infectious Diseases*, 179(Suppl. 1): S188–S191.
31. Johnson, R.F., Dodd, L.E., Yellayi, S. et al. 2011. Simian hemorrhagic fever virus infection of rhesus macaques as a model of viral hemorrhagic fever: clinical characterization and risk factors for severe disease. *Virology*, 421(2): 129–140.
32. Hutchinson, K.L., Villinger, F., Miranda, M.E., Ksiazek, T.G., Peters, C.J. and Rollin, P.E. 2001. Multiplex analysis of cytokines in the blood of cynomolgus macaques naturally infected with Ebola virus (Reston serotype). *Journal of Medical Virology*, 65(3): 561–566.
33. Gupta, M., Macneil, A., Reed, Z.D., Rollin, P.E. and Spiropoulou, C.F. 2012. Serology and cytokine profiles in patients infected with the newly discovered Bundibugyo Ebolavirus. *Virology*, 423(2): 119–124.
34. Macneil, A., Farnon, E.C., Wamala, J. et al. 2010. Proportion of deaths and clinical features in Bundibugyo Ebola virus infection, Uganda. *Emerging Infectious Diseases*, 16(12): 1969–1972.
35. Ergonul, O., Tuncbilek, S., Baykam, N., Celikbas, A. and Dokuzoguz, B. 2006. Evaluation of serum levels of interleukin (IL)-6, IL-10, and tumor necrosis factor-alpha in patients with Crimean–Congo hemorrhagic fever. *Journal of Infectious Diseases*, 193(7): 941–944.
36. Kaya, S., Elaldi, N., Kubar, A. et al. 2014. Sequential determination of serum viral titers, virus-specific IgG antibodies, and TNF-alpha, IL-6, IL-10, and IFN-gamma levels in patients with Crimean–Congo hemorrhagic fever. *BMC Infectious Diseases*, 14: 416.
37. Bente, D.A., Alimonti, J.B., Shieh, W.-J. et al. 2010. Pathogenesis and immune response of Crimean–Congo hemorrhagic fever virus in a STAT-1 knockout mouse model. *Journal of Virology*, 84(21): 11089–11100.
38. Zivcec, M., Safronetz, D., Scott, D., Robertson, S., Ebihara, H. and Feldmann, H. 2013. Lethal Crimean–Congo hemorrhagic fever virus infection in interferon alpha/beta receptor knockout mice is associated with high viral loads, proinflammatory responses, and coagulopathy. *Journal of Infectious Diseases*, 207(12): 1909–1921.
39. Bozza, F.A., Cruz, O.G., Zagne, S.M. et al. 2008. Multiplex cytokine profile from dengue patients: MIP-1beta and IFN-gamma as predictive factors for severity. *BMC Infectious Diseases*, 8: 86.
40. Jain, A., Pandey, N., Garg, R.K. and Kumar, R. 2013. IL-17 level in patients with Dengue virus infection & its association with severity of illness. *Journal of Clinical Immunology*, 33(3): 613–618.
41. Puerta-Guardo, H., Raya-Sandino, A., Gonzalez-Mariscal, L. et al. 2013. The cytokine response of U937-derived macrophages infected through antibody-dependent enhancement of dengue virus disrupts cell apical-junction complexes and increases vascular permeability. *Journal of Virology*, 87(13): 7486–7501.
42. Tassaneetrithep, B., Burgess, T.H., Granelli-Piperno, A. et al. 2003. DC-SIGN (CD209) mediates dengue virus infection of human dendritic cells. *Journal of Experimental Medicine*, 197(7): 823–829.
43. Wang, L., Chen, R.F., Liu, J.W. et al. 2011. DC-SIGN (CD209) Promoter -336 A/G polymorphism is associated with dengue hemorrhagic fever and correlated to DC-SIGN expression and immune augmentation. *PLoS Neglected Tropical Diseases*, 5(1): e934.
44. Xavier-Carvalho, C., Gibson, G., Brasil, P. et al. 2013. Single nucleotide polymorphisms in candidate genes and dengue severity in children: a case-control, functional and meta-analysis study. *Infection, Genetics and Evolution*, 20: 197–205.
45. Marta, R.F., Montero, V.S., Hack, C.E., Sturk, A., Maiztegui, J.I. and Molinas, F.C. 1999. Proinflammatory cytokines and elastase-alpha-1-antitrypsin in Argentine hemorrhagic fever. *American Journal of Tropical Medicine and Hygiene*, 60(1): 85–89.
46. Heller, M.V., Saavedra, M.C., Falcoff, R., Maiztegui, J.I. and Molinas, F.C. 1992. Increased tumor necrosis factor-alpha levels in Argentine hemorrhagic fever. *Journal of Infectious Diseases*, 166(5): 1203–1204.
47. Dejean, C.B., Ayerra, B.L. and Teyssie, A.R. 1987. Interferon response in the guinea pig infected with Junin virus. *Journal of Medical Virology*, 23(1): 83–91.
48. Mahanty, S., Bausch, D.G., Thomas, R.L. et al. 2001. Low levels of interleukin-8 and interferon-inducible protein-10 in serum are associated with fatal infections in acute Lassa fever. *Journal of Infectious Diseases*, 183(12): 1713–1721.

49. Schmitz, H., Kohler, B., Laue, T. et al. 2002. Monitoring of clinical and laboratory data in two cases of imported Lassa fever. *Microbes and Infection*, 4(1): 43–50.
50. Ignatyev, G.M., Agafonov, A.P., Streltsova, M.A., Kashentseva, E.A., 1996a. Inactivated Marburg virus elicits a nonprotective immune response in Rhesus monkeys. J. Biotechnol. 44, 111–118.
51. Demby, A.H., Chamberlain, J., Brown, D.W.G., Clegg, C.S., 1994. Early diagnosis of Lassa fever by reverse transcription-PCR. J. Clin. Microbiol. 32, 2898–2903.
52. Frolov, A.S., Pika, I.S., Eroshkin, A.M., 1997. ProMSED: protein multiple sequence editor for Windows3.11/95. CABIOS 13, 243–248.
53. Ignatyev, G.M., Agafonov, A.P., Streltsova, M.A., Spirin, G.A., Mainagarova, G.I., Chernii, N.B., 1991. Comparative analysis of some immunological parameters of inactivated Marburg viruses in guinea pigs. Vopr. Virusol. 36, 421–423.
54. Ignatyev, G.M., Streltsova, M.A., Agafonov, A.P., et al., 1994. Immunologic characteristics of guinea pigs with Marburg hemorrhagic fever. Vopr. Virusol. 39, 160–171 (in Russian).
55. Ignatyev, G.M., Streltsova, M.A., Agafonov, A.P., Kashentseva, E.A., Prozorovsky, N.S., 1996c. Experimental study of therapy of Marburg hemorrhagic fever with desferal, ribavirin and homologous interferon. Vopr. Virusol. 41, 206–209.
56. Poljkov, I.V., Sokolova, N.S., 1975. Practice of Medical Statistics. Medicina Press, Leningrad.
57. Bente, D.A., Alimonti, J.B., Shieh, W.J., et al. 2010. Pathogenesis and immune response of Crimean–Congo hemorrhagic fever virus in a STAT-1 knockout mouse model. J. Virol. 84(21), 11089–11100.
58. Kolokoltsova, O.A., Yun, N.E., Poussard, A.L., et al. 2010. Mice lacking alpha/beta and gamma interferon receptors are susceptible to Junin virus infection. J. Virol. 84(24), 13063–13067.
59. Lever, M.S., Piercy, T.J., Steward, J.A., et al. 2012. Lethality and pathogenesis of airborne infection with filoviruses in A129 α/β-/- interferon receptor-deficient mice. J. Med. Microbiol. 61(Pt 1), 8–15.
60. Shresta, S., Sharar, K.L., Prigozhin, D.M., Beatty, P.R., Harris, E. 2006. Murine model for dengue virus-induced lethal disease with increased vascular permeability. J. Virol. 80(20), 10208–10217.
61. Bray, M., Davis, K., Geisbert, T., Schmaljohn, C., Huggins, J. 1999. A mouse model for evaluation of prophylaxis and therapy of Ebola hemorrhagic fever. J. Infect. Dis. 179(Suppl. 1), S248–S258.
62. Connolly, B.M., Steele, K.E., Davis, K.J., et al. 1999. Pathogenesis of experimental Ebola virus infection in guinea pigs. J. Infect. Dis. 179(Suppl. 1), S203–S217.
63. Johnson, R.F., Dodd, L.E., Yellayi, S., et al. 2011. Simian hemorrhagic fever virus infection of rhesus macaques as a model of viral hemorrhagic fever: clinical characterization and risk factors for severe disease. Virology 421(2), 129–140.
64. Fritz, E.A., Geisbert, J.B., Geisbert, T.W., Hensley, L.E., Reed, D.S. 2008. Cellular immune response to Marburg virus infection in cynomolgus macaques. Viral Immunol. 21(3), 355–363.
65. Mohamadzadeh, M., Chen, L., Olinger, G.G., Pratt, W.D., Schmaljohn, A.L. 2006. Filoviruses and the balance of innate, adaptive, and inflammatory responses. Viral Immunol. 19(4), 602–612.
66. Rubins, K.H., Hensley, L.E., Wahl-Jensen, V., et al. 2007. The temporal program of peripheral blood gene expression in the response of nonhuman primates to Ebola hemorrhagic fever. Genome Biol. 8(8), R174.
67. Wauquier, N., Becquart, P., Padilla, C., Baize, S., Leroy, E.M. 2010. Human fatal Zaire Ebola virus infection is associated with an aberrant innate immunity and with massive lymphocyte apoptosis. PLoS Negl. Trop. Dis. 4(10), e837.
68. Hutchinson, K.L., Villinger, F., Miranda, M.E., Ksiazek, T.G., Peters, C.J., Rollin, P.E. 2001. Multiplex analysis of cytokines in the blood of cynomolgus macaques naturally infected with Ebola virus (Reston serotype). J. Med. Virol. 65(3), 561–566.
69. Bradfute, S.B., Warfield, K.L., Bray, M. 2012. Mouse models for filovirus infections. Viruses 4(9), 1477–1508.
70. Warfield, K.L., Bradfute, S.B., Wells, J., et al. 2009. Development and characterization of a mouse model for Marburg hemorrhagic fever. J. Virol. 83(13), 6404–6415.
71. Villinger, F., Rollin, P.E., Brar, S.S., et al. 1999. Markedly elevated levels of interferon (IFN)-gamma, IFN-alpha, interleukin (IL)-2, IL-10, and tumor necrosis factor-alpha associated with fatal Ebola virus infection. J. Infect. Dis. 179(Suppl. 1), S188–S191.
72. Gupta, M., Macneil, A., Reed, Z.D., Rollin, P.E., Spiropoulou, C.F. 2012. Serology and cytokine profiles in patients infected with the newly discovered Bundibugyo Ebolavirus. Virology 423(2), 119–124.
73. Macneil, A., Farnon, E.C., Wamala, J., et al. 2010. Proportion of deaths and clinical features in Bundibugyo Ebola virus infection, Uganda. Emerg. Infect. Dis. 16(12), 1969–1972.
74. Ergonul, O., Tuncbilek, S., Baykam, N., Celikbas, A., Dokuzoguz, B. 2006. Evaluation of serum levels of interleukin (IL)-6, IL-10, and tumor necrosis factor-alpha in patients with Crimean–Congo hemorrhagic fever. J. Infect. Dis. 193(7), 941–944.
75. Kaya, S., Elaldi, N., Kubar, A., et al. 2014. Sequential determination of serum viral titers, virus-specific IgG antibodies, and TNFalpha, IL-6, IL-10, and IFN-gamma levels in patients with Crimean–Congo hemorrhagic fever. BMC Infect. Dis. 14, 416.