

Marburg, Junín, Machupo, and Kyasanur Forest Disease Viruses: Etiology, Epidemiology, Chemical Architecture, Morphological Fingerprinting, Biomolecular Pathogenesis, Arenaviruses, Orthoflaviviruses, BSL-4 Protocols

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Abstract

The zoonotic importance of Viral hemorrhagic fevers (VHFs) is well documented for Marburg virus (MARV), Junín virus (JUNV), Machupo virus (MACV), and Kyasanur Forest Disease virus (KFDV) due to their high morbidity, mortality, and potential to cause epidemics. Although the above-mentioned viruses are members of different virus families, they have some common pathogenic features such as zoonosis, dysregulation of immunity, endothelial damage, and systemic illness. This review presents an analysis of their causes, prevalence, chemical structure, morphological identification, biochemical etiology, diagnostic techniques, treatment methods, and Biosafety Level-4 (BSL-4) laboratory techniques. Focus is made on human clinical, molecular, and epidemiological data, and less is emphasized on animal experiments. The latest molecular techniques of diagnostics, genome-wide monitoring, vaccine research, anti-viral agents and biosafety measures have helped in detecting and preparing for any outbreak of such diseases. But absence of specific treatments, lack of monitoring in endemic areas, and lack of laboratory facilities still present a challenge for controlling these diseases. In addition, the review identifies research deficiencies existing in today's scientific field and stresses the necessity of applying One Health principles, international cooperation, developing biosafety capacity and conducting more human-oriented research on VHFs.

Keywords: Marburg virus (MARV); Junín virus (JUNV); Machupo virus (MACV); Kyasanur Forest Disease virus (KFDV); Viral hemorrhagic fever; Biomolecular pathogenesis; BSL-4 biosafety; One Health.

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1. INTRODUCTION

VHFs are serious zoonotic infections caused by RNA viruses which can result in fever, hemorrhages, coagulopathy, and multiple organ system failure. The MARV, JUNV, MACV, and KFDV are significant emerging/reemerging zoonotic pathogens due to their epidemic capabilities, mortality rate, and lack of treatment¹. These viruses are part of the Filoviridae, Arenaviridae, and Ortho Flaviviridae families but share common characteristics of being zoonotic, causing immunodysfunction, and causing severe infections in humans.

Outbreaks of Marburg viral diseases in Africa and the endemic prevalence of Argentine hemorrhagic fever, Bolivian hemorrhagic fever, and KFDV underscore the significance of these diseases in public health. Factors such as climate change, deforestation, increased interaction between humans and wildlife, and globalization pose increasing threats of spillover infections². Scientific advances in molecular diagnosis, genomic surveillance, and structural virology have enhanced our knowledge about these viruses, although lack of antiviral drugs is a challenge.

This review discusses the pathogenesis, epidemiology, chemistry, structure, molecular mechanisms of disease causation, diagnosis, management, and biosafety aspects of all four viruses. Human clinical, molecular, and epidemiological studies have priority, while animal experiments have been used minimally³. This review also highlights important gaps and future directions in virus research.

1.1 Background and Context

Viruses like MARV, Junín JUNV, MACV, and KFDV are all zoonotic RNA viruses that lead to severe cases of hemorrhage. MARV is found in Africa, JUNV and MACV are indigenous to Argentina and Bolivia, while KFDV is predominantly found in the forests of India. Despite differences in taxonomical and transmission characteristics, these viruses can cause fever, vascular damage, problems with coagulation, neurological symptoms, and even organ failure. Increased use of molecular diagnostics and genomics has provided more insight into their biology, but there still remain treatment limitations and surveillance difficulties⁴.

1.2 Objectives of the Review

The objectives of this review are:

- To investigate the origin, classification, natural reservoir, transmission and epidemiology of the four viruses.
- To compare their genetic material, proteins, envelope, glycoproteins (GP), and virion structure.
- To understand viral entry, replication, immune evasion, cytokine deregulation and tissue damage.

- To evaluate present diagnostic approaches, treatment and vaccines available.
- To understand Biosafety level 4 lab requirements and specimen handling and decontamination techniques.
- To identify research gaps based on human evidence mostly.

1.3 Importance of the Topic

Importance of studying these viral agents is that they have the potential to cause serious disease, local outbreaks, and disrupt the health care system. Changes in ecological factors, deforestation, climate variation, and greater interaction with wildlife and vectors may increase the chances of further spill-over events in the future⁵. Early symptoms of these viruses can be confused with other febrile illnesses, making it difficult for their identification and quarantine. Further, lack of therapeutic options and vaccinations against them, along with containment of these viruses in laboratories, creates problems.

2. ETIOLOGY, EPIDEMIOLOGY, AND STRUCTURAL BIOLOGY

The four viral pathogens considered in this review include MARV, JUNV, MACV, and KFDV. These viral pathogens are zoonotic RNA viruses, which result in viral hemorrhagic fever diseases in human beings. Even though these four viruses do not belong to the same viral family, they have several features in common, such as having animal reservoirs, being highly pathogenic, and causing local outbreaks. The continuous emergence of these viruses is influenced by the ecological changes, globalization, and the interaction between human beings and wildlife animals⁶.

2.1 Etiology, Taxonomy, and Epidemiology

The MARV belongs to the Filoviridae family and MARV genus while the JUNV and the MACV belong to the family of Arenaviridae and Mammarenavirus genera. On the other hand, the KFDV belongs to the Ortho Flaviviridae family and Flavivirus genus. While these four viruses contain single-stranded RNA genome, they vary in genome structure, modes of transmission and evolution⁷. Molecular genetics and genomics studies on these viruses have greatly enhanced knowledge on their genetic variations and phylogeny.

The epidemiology of these viruses is directly tied to the natural hosts of the pathogens. The natural host for MARV is the Egyptian fruit bat (*Rousettus aegyptiacus*), which has been associated with MARV outbreaks in many African nations. JUNV is prevalent in Argentina while MACV is predominant in Bolivia through rodents. KFDV is indigenous to the Western Ghats of India. Transmission of the disease happens via *Haemaphysalis* ticks and wildlife hosts. Infection in humans is usually because of direct contact with infected animals, tick bites, or bodily fluids of the infected individuals⁸.

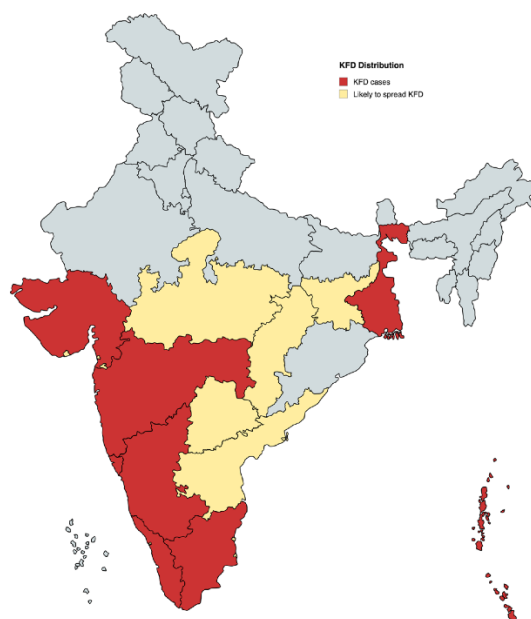


Figure 1. Geographic Distribution of Kyasanur Forest Disease Virus (KFDV) in India
Showing Endemic and Potential Spread Regions

The recent epidemics highlight the fact that the changes in climate, deforestation, land use change, and greater interaction between man and animals have all played an important role in the development of such viral infections. Late detection, limited laboratory facilities, and lack of proper infection control methods have often been the cause behind an epidemic outbreak. While MARV has the ability to spread effectively through direct contact with infected body fluids, Junín and MACV are more commonly found through exposure to infected rodents' feces⁹. On the other hand, KFDV is largely tick-borne with no recorded cases of human-to-human transmission.

2.2 Chemical Architecture and Morphological Fingerprinting

The structural composition of MARV, JUNV, MACV, and KFDV plays an important role in their infectivity, host preference, and pathogenicity. While the four viruses are from different viral families, they share some common structures, such as lipid envelope, GPs on the surface, and single-stranded RNA as genome. Recent developments in cryo-electron microscopy, X-ray crystallography, and molecular virology have greatly enhanced our knowledge about their structural composition. The knowledge about the structure helps us learn how these viruses attach, replicate, and trigger immune response, and helps to design drugs against them.

The MARV has a single non-segmented negative-strand RNA genome of about 19 kb that has seven structural proteins including NP, VP35, VP40, GP, VP30, VP24, and RNA-dependent

RNA polymerase (L). On the other hand, the Junín and Machupo viruses have two segment ambisense RNA genomes made up of S and L segments that code for nucleoproteins, GP precursors, matrix proteins, and viral polymerases¹⁰. The KFDV has a positive-sense single-stranded RNA genome of about 11 kb that codes for a single polyprotein, which is further processed to yield structural and non-structural proteins. Even though the four viruses differ in genome structure and composition, they all rely on host cells to replicate their genomes and synthesize proteins.

The envelope of the virus is mainly derived from the membrane of the host cell and consists of surface GPs which facilitate receptor binding and membrane fusion. The MARV expresses one GP which binds the host cell receptors and helps in facilitating viral entry via endosome pathway. The Junin and Machupo viruses use GP1 and GP2 GP complex for the recognition of cellular receptors while the KFDV encodes envelope (E) and membrane (M) proteins as found in flaviviruses¹¹.

Morphologically, MARV shows a distinct filamentous structure with pleomorphic forms that can be long, curved, or branched. However, JUNV and Machupo virus show a distinct spherical to pleomorphic envelope form, with ribosomes inside the virions, producing a unique granular appearance seen under electron microscopy. On the other hand, KFDV is relatively smaller and shows a unique spherical form with an icosahedral nucleocapsid surrounded by a lipid envelope¹². This is because of its morphology that distinguishes it from the rest of the viruses mentioned above, which belong to the arenavirus family.

2.3 Biomolecular Pathogenesis

In case of MARV, JUNV, MACV, and KFDV, the molecular pathogenesis of these diseases entails the interaction between viral replication and the response of the immune system of the host. Even though the above-mentioned viral pathogens are not part of the same family of viruses, their strategies in initiating the disease, immune escape, and causing systemic inflammation are relatively similar. The seriousness of the disease is dependent on the viral burden, immune dysregulation, endothelial cell damage, and level of tissue injury¹³.

Infection starts by the binding of viral GPs to host cell receptors, which are found in macrophages, dendritic cells, endothelial cells, and monocytes. Once binding takes place, the viral RNA genome is liberated into the cytoplasm for replication and synthesis of the new viral proteins. Viral proteins are assembled to form new virions and finally liberated to infect other cells¹⁴. Rapid replication leads to dispersal in the blood and lymph, thus making it possible for the virus to infect other organs like the liver, spleen, lymph nodes, kidneys, and endothelium.

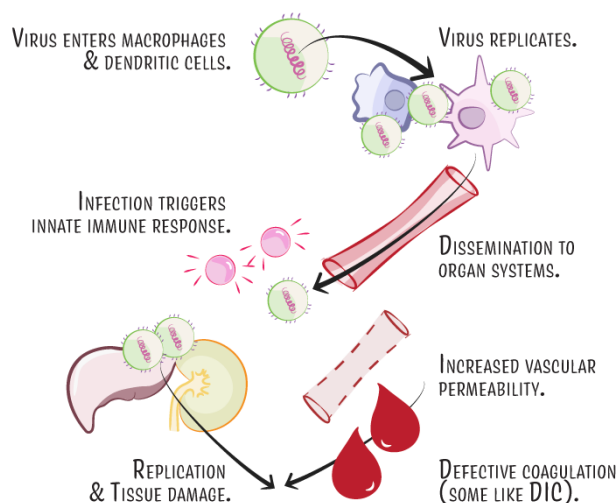


Figure 2. General Biomolecular Pathogenesis of Viral Hemorrhagic Fever Viruses

With progression of infection, dysregulation of the host immune system increases. Clinical observations have demonstrated that severe infection is characterized by an abnormal production of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and interferon- γ (IFN- γ)¹⁵. This inflammatory activity causes development of endothelial dysfunction, increased vascular permeability, problems with coagulation, and bleeding complications. At the same time, these viruses disrupt signaling pathways involved in the immune responses of the body, thereby preventing the interferon antiviral effect and facilitating further virus replication.

The progressive process of viral replication and the injury caused by the immune response results in widespread tissue and organ damage. Pathological studies conducted in humans have shown evidence of hepatic necrosis, depletion of splenic lymphoid tissue, renal dysfunction, and endothelial damage in patients with hemorrhagic fever caused by viruses. In the late stages of the illness, disseminated intravascular coagulation, circulatory shock, and multi-organ failure often result in death¹⁶. Elevated liver enzyme levels, thrombocytopenia, leukopenia, inflammation cytokines, and disturbances in coagulation are some of the clinical markers associated with the progression of the disease.

Table 1. Comparative Characteristics of Marburg, Junín, Machupo, and Kyasanur Forest Disease Viruses

Parameter	Marburg Virus	Junín Virus	Machupo Virus	Kyasanur Forest Disease Virus
Family	Filoviridae	Arenaviridae	Arenaviridae	Orthoflaviviridae

Genome	Negative-sense ssRNA	Ambisense ssRNA	Ambisense ssRNA	Positive-sense ssRNA
Natural Reservoir	Egyptian fruit bat	Calomys musculus	Calomys callosus	Small mammals
Primary Transmission	Body fluids	Rodent excreta	Rodent excreta	Tick bites
Geographic Distribution	Africa	Argentina	Bolivia	India
Incubation Period	2–21 days	6–14 days	7–14 days	3–8 days
Case Fatality Rate	24–88%	15–30%	20–35%	3–10%
Major Clinical Features	Hemorrhagic fever	Hemorrhagic fever	Hemorrhagic fever	Fever with hemorrhagic manifestations

3. DIAGNOSTIC ADVANCES, THERAPEUTIC STRATEGIES, BIOSAFETY, AND FUTURE DIRECTIONS

Successful management of MARV, JUNV, MACV, and KFDV is based on proper diagnosis, clinical management, strict biosafety measures, and research on more effective treatment strategies¹⁷. Even though there have been substantial developments in molecular diagnostic techniques and supportive care, lack of globally effective antiviral medications for a number of viral hemorrhagic fever viruses poses serious public health problems. Technological innovations, development of vaccines, and biosafety measures have enhanced global preparedness against such infections; nonetheless, ongoing monitoring and interdisciplinary collaboration is critical for the control of the diseases.

3.1 Diagnostic and Therapeutic Advances

An accurate and timely diagnosis is very important in order to enhance the outcome for patients and minimize the risk of spreading the infection. The molecular tools like reverse transcription-polymerase chain reaction (RT-PCR) have remained the gold standard method for detection of RNA viruses during the acute phase of infection due to its superior sensitivity and specificity¹⁸. Other laboratory methods like enzyme-linked immunosorbent assay (ELISA), immunofluorescent tests, viral isolation, and next generation sequencing have also been used in diagnostic procedures. These technologies help in the quick detection of viral strains¹⁹.

Management of these infections largely relies on supportive treatment designed to maintain proper body fluid and electrolyte balance, adequate oxygenation, and hemodynamic stability. Timely medical treatment helps to prevent shock, massive bleeding, and multiple organ dysfunction syndrome. Although the number of antiviral treatments is rather small, investigational drugs such as remdesivir, favipiravir, ribavirin, and monoclonal antibodies exhibit different levels of efficacy against specific VHF. The effectiveness of these drugs greatly varies depending on the virus causing infection²⁰.

The recent advancements in biomedical studies have led to faster development of vaccines, antiviral agents that specifically target viruses and diagnostic technologies. Promising findings have been reported through human clinical trials in the development of vaccines for the MARV infection, and the Candid #1 vaccine has greatly reduced the cases of Argentine hemorrhagic fever caused by JUNV infection²¹. Further studies on MACV and KFDV are currently concentrating on the development of more effective vaccines and antivirals for these viruses, as well as point-of-care diagnostics.

3.2 BSL-4 Laboratory Protocols and Biosafety

It is critical that MARV, JUNV, MACV, and KFDV be handled through strict biosafety protocols to protect the laboratory staff, health care providers, and the environment around them. Since these pathogens pose the potential for severe or even fatal disease, all procedures involving these viruses in laboratories should be carried out in accordance with appropriate biosafety protocols. International organizations such as the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) have developed standard biosafety protocols²².

Facilities like high-containment laboratories are characterized by the use of engineering control measures that reduce the chances of pathogens escaping from the lab. Engineering control measures used include negative air pressure systems, HEPA-filtered air handling systems, restricted access control areas, airtight labs, and environmental monitoring systems²³. The use of engineering controls ensures that any infectious aerosol particles are confined in lab facilities.

The laboratory staff receive extensive biosafety training before working with infectious samples. Scientists working in BSL-4 laboratories wear positive pressure suits or other personal protective equipment (PPE), which is dependent on the layout and procedure of that particular laboratory²⁴. Samples suspected of carrying these viruses are transferred using the internationally approved triple packaging system²⁵.



Figure 3. BSL-4 Laboratory Practices for Handling High-Consequence Viral Hemorrhagic Fever Pathogens

Good laboratory practices go beyond issues of infrastructure and personnel safety in the form of standard protocols for the preparation of specimens, culturing of viruses, equipment disinfection, and waste management²⁶. Chemical disinfectants, methods of sterilization, and autoclave treatment are commonly used to ensure that pathogens are rendered non-infective prior to disposal. Ongoing biosafety monitoring, contingency plans, and personnel training provide increased laboratory safety measures in case of a public health emergency²⁷.

3.3 Current Challenges and Future Perspectives

Despite all the progress that has been made in diagnosing, treating, and biosafety measures for VHF, some obstacles remain that pose problems for the effective management of the diseases²⁸. There are a number of endemic areas where there are delays in diagnoses, poor laboratory facilities, lack of adequate medical facilities, and poor disease surveillance mechanisms. Environmental changes, encroachment by humans into the natural habitats of animals, globalization, and climatic variations have added to the number of opportunities for zoonotic outbreaks²⁹.

Another one of the biggest challenges faced by the field includes the lack of availability of sophisticated diagnostic facilities and special care centers in the endemic areas. Delayed laboratory confirmation makes clinical management of such outbreaks difficult and further increases the chances of disease transmission³⁰. Improvement in healthcare facilities, surveillance systems, and increased access to molecular diagnostic tools continues to be important for better preparedness against outbreaks³¹.

Technological advancements in recent years have brought about a change in the way surveillance and monitoring of high consequence viruses are carried out. Genomic surveillance, next generation sequencing, digital epidemiology, artificial intelligence, and machine learning

are becoming part of outbreak investigation processes and can help in identifying pathogens and predicting risks³².

The future research direction should focus on the development of broad-spectrum antiviral drugs, improved generation vaccines, point of care diagnostic technologies, and management protocols. More attention should be paid to the conductance of multicenter human trials, discovery of biomarkers, data sharing between nations, and One Health approach³³. Further improvement of biosafety facilities, translational research, and global surveillance systems will be key elements to enhance preparedness for the future occurrence of viral hemorrhagic fever outbreak.

Table 2. Comparative Analysis of Recent Studies on Biosafety and Laboratory Preparedness for VHF

Reference	Study Focus	Key Findings	Contribution to the Present Review
Turbett et al. (2024) ³⁴	Laboratory preparedness and diagnostic readiness for suspected VHFs	Developed a comprehensive laboratory toolkit emphasizing specimen handling, diagnostic workflows, risk assessment, and biosafety practices for suspected VHF cases.	Highlights the importance of standardized laboratory preparedness and diagnostic protocols for early detection and safe management of Marburg, JUNV, MACV, and KFDV.
Uppala et al. (2025) ³⁵	MARV pathogenesis and global public health strategies	Reviewed the molecular pathogenesis, transmission dynamics, outbreak response, and public health interventions for MARV disease.	Provides updated evidence on MARV biology, outbreak management, and international preparedness strategies relevant to emerging VHFs
Weidmann et al. (2016) ³⁶	Biosafety standards for high-risk viral hemorrhagic fever laboratories	Proposed standardized biosafety recommendations for handling highly pathogenic hemorrhagic fever viruses under high-containment laboratory conditions.	Supports discussion of internationally accepted biosafety principles and laboratory containment measures applicable to handling highly pathogenic zoonotic viruses.

Wurtz et al. (2016) ³⁷	Global survey of laboratory-acquired infections in BSL-3 and BSL-4 laboratories	Identified causes of laboratory-acquired infections and emphasized strict adherence to biosafety regulations, personnel training, and risk management.	Demonstrates the importance of biosafety compliance, occupational safety, and continuous training for preventing laboratory-associated infections during viral research.
Xia et al. (2019) ³⁸	BSL-4 laboratory training and competency development	Described a structured BSL-4 training program integrating theoretical instruction, simulation exercises, and practical competency assessment for laboratory personnel.	Reinforces the role of specialized training, competency evaluation, and operational preparedness in maintaining safe high-containment laboratory practices.

4. DISCUSSION

A comparison of MARV, JUNV, MACV, and KFDV reveals that, although they belong to diverse viral families, there are many similarities among them such as being zoonotic pathogens, having RNA genomes, causing severe systemic disease, dysregulating immunity, and having the capability to cause an outbreak. There are many differences between them such as their reservoirs, mode of transmission, geographical distribution, genome structure, structural proteins, and clinical manifestations³⁹. These differences have a direct impact on surveillance, diagnosis, treatment, and biosafety issues. The current evidence suggests that early molecular diagnosis, supportive care, and high containment laboratory readiness are very crucial.

4.1 Interpretation and Analysis of Findings

The results have shown that the complexity of the biology of these viruses necessitates the adoption of different strategies for each virus, rather than one general strategy. While the MARV is usually related to bat reservoirs and person-to-person spread via bodily fluids, the JUNV and MACV are associated with rodent contact. KFDV is distinct since it is mostly transmitted via infected ticks⁴⁰. There are structural variations in terms of genome structure, GP coating, and virion structure as well, which determine how the virus enters cells, replicates itself, evades the immune system, and induces disease. All four infections have severe manifestations due to uncontrollable viral replication, immune response, damage to endothelial cells, and coagulation disorders.

4.2 Implications and Significance

Conclusions drawn from the review have far-reaching consequences for medical science, laboratory diagnostics and public health readiness. Immediate diagnosis through RT-PCR, appropriate medical care and isolation are key to preventing the development of complications and spreading of the virus. Successful vaccination with Candid #1 against Junín is an example of how significant targeted vaccination can be, but research on vaccines and antiviral drugs for Marburg, MACV and KFDV are still needed. Moreover, it is stressed that biosafety is possible only through laboratory facilities and well-trained staff.

4.3 Research Gaps and Limitations

Among the main limitations in the field are the lack of sufficient human clinical trials, low numbers of patients involved, inconsistency in describing biomarkers and a lack of comparative research between the four viruses. Information about virus-specific antivirals, monoclonal antibodies, and vaccines is also incomplete especially regarding MACV and KFDV. In addition, there are limited abilities to conduct diagnostic and surveillance in certain endemic areas, which affects the quality of the epidemiology information. Another restriction is the lack of human molecular and pathological evidence compared to animal studies, so that is why this review focused on human evidence but sometimes used molecular data too.

4.4 Future Research Directions

The focus of future studies should be on multicenter studies involving humans, standardization of clinical data sets, and evaluation of diagnostic, treatment, and vaccination approaches prospectively. The need to pay attention to fast point-of-care testing, broad-spectrum antivirals, cross-protecting monoclonal antibodies, more effective vaccination platforms, and biomarker identification that can predict the severity of the disease is urgent. Genomic surveillance, artificial intelligence, digital epidemiology, and One Health approaches should be applied for the sake of improving early detection and prediction of outbreaks. High-containment facilities in different regions, workforce education, international collaboration, and harmonization of biosafety standards are also needed.

5. CONCLUSION

MARV, JUNV, MACV, and KFDV are still significant zoonotic viruses due to their ability to cause severe hemorrhagic fever, outbreaks, and significant disruption to public health. Despite the differences among these four viruses in terms of taxonomy, reservoirs, mode of transmission, structure, and geographic location, they all have similar aspects regarding their pathogenesis. These involve the ability to evade immunity, inflammation, vascular damage, and organ injury. Control of these diseases requires early detection, supportive treatment, better vaccines and anti-viral drugs, as well as surveillance and biosafety measures. Thus, clinical studies in humans, One Health approach, genomics, and investment in high containment facilities are important.

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