REVIEW ARTICLE

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Arenaviruses and Hemorrhagic Fevers: Virology, Pathogenesis, Ecology, and Global Control Strategies

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ABSTRACT

Arenaviruses are a genus of enveloped, negative-sense or ambisense RNA viruses within the family *Arenaviridae*, known as significant zoonotic pathogens causing severe hemorrhagic fevers in humans. The virions are spherical and pleomorphic, ranging from 60–300 nm in diameter, and contain host-derived ribosomes, giving them a sandy ("arena") appearance. Their genome has two single-stranded RNA segments—the small (S) and large (L) segments—using an ambisense coding strategy to encode four main proteins: nucleoprotein (NP), glycoprotein precursor (GPC), RNA-dependent RNA polymerase (L), and matrix protein (Z). Arenaviruses persist in specific rodent reservoirs, forming two major complexes: the Old World (e.g., Lassa, Lujo viruses) and the New World (e.g., Junin, Machupo, Guanarito viruses). Human infection occurs mainly through inhalation of aerosols or contact with fomites contaminated with rodent excreta. Clinical manifestations range from mild febrile illness to severe viral hemorrhagic fever (VHF) with high fever, coagulopathy, vascular leakage, and multi-organ failure. Diagnosis requires biosafety level 4 (BSL-4) containment and relies on serology (ELISA, IFA), reverse transcription-polymerase chain reaction (RT-PCR), or virus isolation. Treatment is supportive, though ribavirin shows limited efficacy for Lassa and Junin viruses when given early. Prevention focuses on rodent control, public health education, and infection control in healthcare settings. Despite promising vaccine candidates, none are commercially available, underscoring arenaviruses as persistent and emerging global health threats.

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Keywords
Arenavirus, Viral Hemorrhagic Fever, Lassa Fever, Zoonosis, Ambisense RNA, Rodent Reservoir, Ribavirin, Biosafety Level 4, One Health, Emerging Infectious Disease

1. Introduction

An arenavirus is a virus which is a member of the family *Arenaviridae*. Those viruses infect rodents and occasionally humans, arenaviruses have also been discovered which infect snakes. At least eight arenaviruses are known to cause human disease. The diseases derived from arena viruses range in security. Aseptic meningitis, a severe human disease that causes *inflammation* covering the brain and spinal cord, can arise from the lymphocytic *Choriomeningitis virus* (LCMV) infection. Hemorrhagic fever syndromes are derived from infections such as *GuanaritoVirus* (GTOU), *Juninvirus* (JUNU) *Lassavirus* (LASU) *Lujovirus* (LUJU) (Briese *et al*., 2009), machupovirus (MACU), Sobia virus (SABV)or white waterb*Arrouovirus*(WWAU) (Botten *et al*., 2010).

Arenaviruses can be divided into two serogroups, which are different genetically and by geographical distribution: (Delgado *et al*., 2008) when the virus is classified "old world" this means it is found in the Eastern Hemisphere in places such as Europe, Asia and Africa. When it is found in the Western Hemisphere in places such as Argentina, Bolivia, Venezuela, Brazil, and the United States, it is classified as "New World" Lymphocytic choriomeningitis (LCM) virus is the only Arenavirus to exist in both areas but is classified as an old world virus.

A third group of viruses has been described from snakes (stenglenin *et al*., 2012). The organization of the genome is typical of arenaviruses but their glycoproteins resemble those of filoviruses.

1.1 Genome Nature

Arenaviruses have a segmented RNA genome that consists of two single-stranded ambisense RNAs (Ano *et al*., 1976). As with all negative senses RNA alone is not infectious and the virus replication machinery is required to initiate infection within a host cell (Lee *et al*., 2000). Genomic sense sense RNA packaged into the arenavirus virion is designated negative sense RNA, and must first be copied into a positive sense mRNA in order to produce viral protein.

1.2 Virus Classification

Group: Group V (−ssRNA) — Negative-sense single-stranded RNA viruses
Order: Unassigned
Family: *Arenaviridae*
Genus: *Mammarenavirus*

Old World (LCMV–Lassa virus complex):
Lassa virus
Lymphocytic choriomeningitis virus (LCMV)
Morogoro virus

New World (Tacaribe virus complex):
Chapare virus
Flexal virus
Guanarito virus
Junin virus
Machupo virus

Other Members:
Reptarena virus

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2. Structure of the Virus

Viewed in cross section, arenaviruses contain grainy particles that are ribosomes acquired from their host cells (Fig. 1). It is from the characteristic that they acquired the Arenavirus from the latinroot meaning sand. The ribosomal structures are not believed to be essential for virus replication. Virus particles, orvirions, are pleomorphic (variable in shaped) but are spherical with a diameter of 60-300nm, andare covered with surface glycoprotien spikes (Emonent *et al*., 2011). The virus contains abraded nucleocapsid with two single stranded RNA segments. The nucleocapsid with two single stranded RNA segments. The nucleocapsidcosists of a core of nucleic acid enclosed in a protein coat. Although they are often miscategorized a negative sense viruses, arena viruses are ambisense. This confusion stems from the pacts that while sections of their genome are considered negative sense, and encodes genes in the reverse direction, other sections encoder genes in the opposite (forward/positive sense) direction. This complex gene expression structure is theorized to be a primitive regulatory system, allowing the virus to control what contains are synthesized at what point into life cycle. The life cycle of the arenavirus is instructed to the cell cytoplasm.

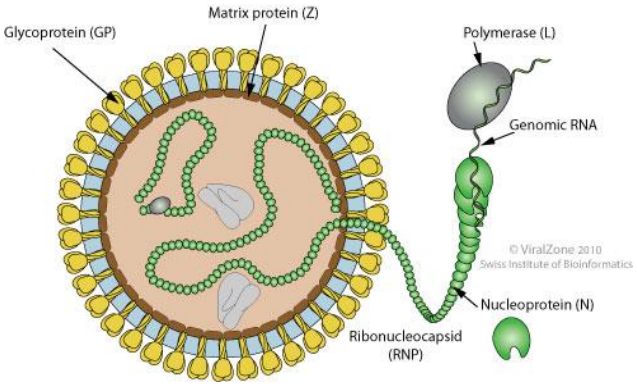

Figure 1: Envelope spherical Diameter from 60-300nm
Source: http://viral zone.expasy.org/resource

2.1 Genetic Basic

Proteins for virulent and adaptation.

The small segment (s) encodes the glycoprotein precursor (Gpc) and the nucleocapsid protein (NP) that are the most important immunogens of the virus (Figs. 2 and 3). The NP and Gpc sequences are seperated by a non codingintergenic region (IGR) (Auper*net al*., 1984). The GPC (glycoprotein procecursor) function to mediate viral assembly,entry and encoatingand to determine cell tropism.NP has multiple function: it Encapsidates the arena virus genome segments, interacts with Lprotein to form the RNP core for RNA replication and transcription, associated with with Z protein for viral assembly, plays an important role in suppressing the innate immune response, and has exonuleaseand nucleotide binding activating (pinschewer *et al*., 2003., Eichler *et al* ; 2003., Casabona *et al* ., 2009; Shranko *et al*., 2010., Martinez *et al*., 2006., Martinez *et al*., 2009., Hastie *et al* ., 2011 Q1 *et al* ., 2010).

The large (L) segment (-7.2kb) encodes the small zinc-binding protien (z) that functions as a matrix protein, interacts with L and andNp and other host protein plays arole in viral transcription and replication has pro-apoptotic activity and is essential for virus budding (Shranko *et al* ., 2010, Compbell *et al*., 2000., Kentsis *et al* 2006).

The L- segment also encodes the L- protein that is an RNA dependent RNA polymerase (RdRp). L and NP are the minimal transacting virus factors required for replication and transcription (Pinschewer *et al*., 2003, Lee *et al*., 2000., Lopee *et al* ., 2001). (figure 2) L and 2 are also separated by an IGR. Both RNA segments are flanked by noncoding region (UTR) thatfunction with the LGR as cis-acting elements for RNA replication and transcription.

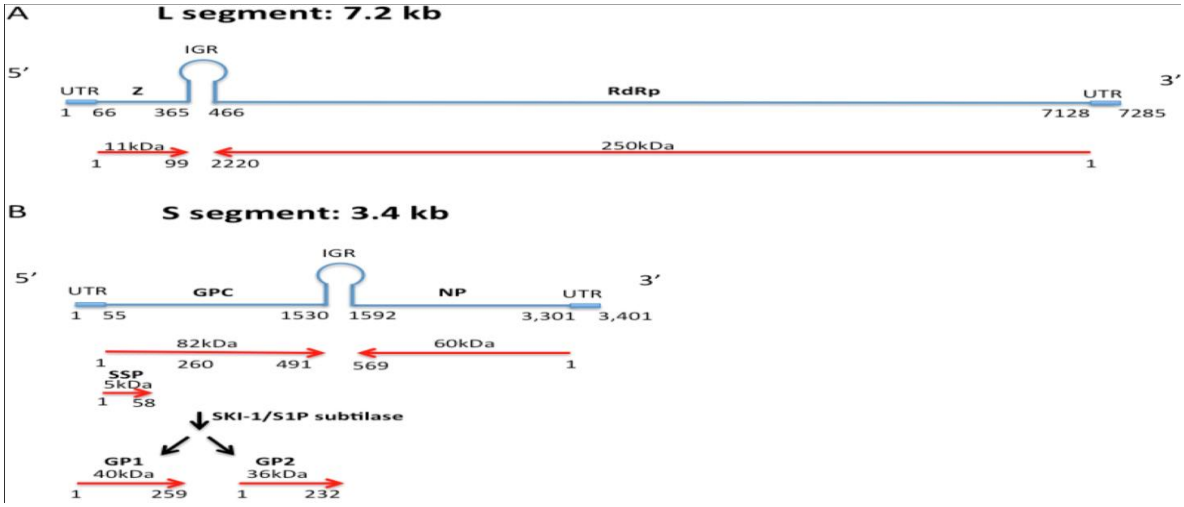

Figure 2: Arena virus genome structure from 5’ to 3’ end
Source: www.mdpi.com/viruses/viruses-05-00241/article-deploy/htm/image/viruses-05-00241-goo1.png

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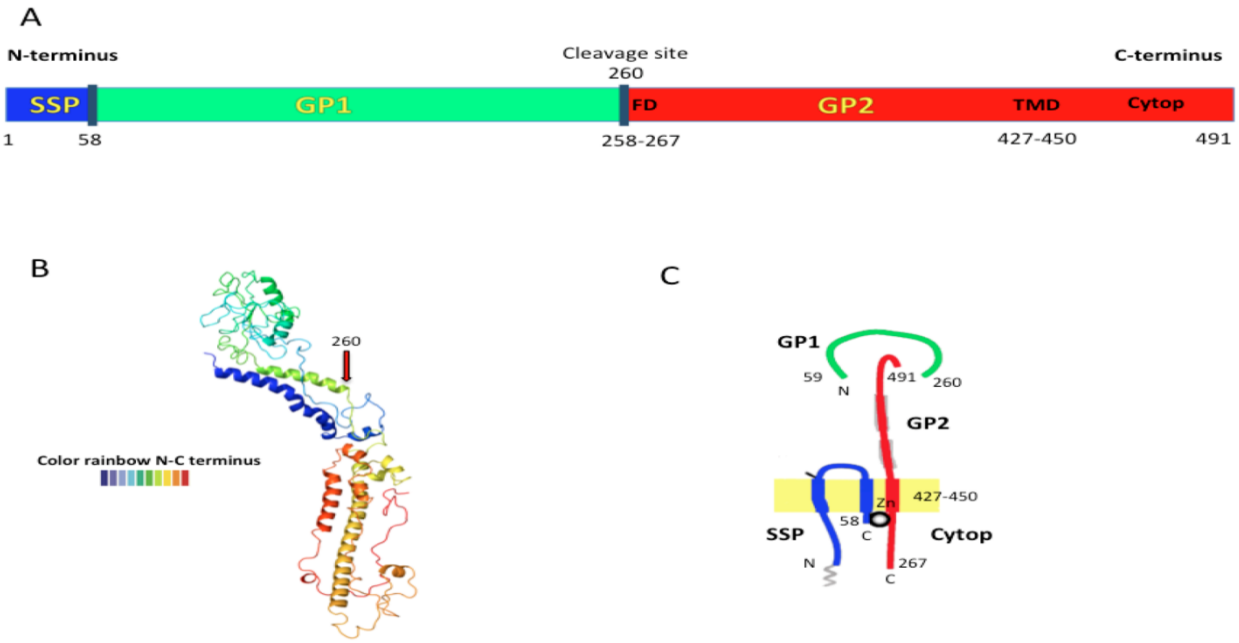

Figure 3: The LASV envelop glycoprotein precursor (GPC) structure
Source: www.mdp:com/viruses/viruses-05-00241/article-deploy/html/images/virus-05-00241-g001.png

Viral replication of Arena Virus
Their replication cycle is tightly linked to their unique **ambisense genome organization**, which encodes proteins in both negative- and positive-sense orientations. Understanding the replication of arenaviruses provides crucial insights into viral pathogenesis and opportunities for therapeutic development (Salvato and Shimomaye, 1989; Buchmeier et al., 2007).

1. Attachment and Entry
- Arenaviruses initiate infection by attaching to host cell receptors.
- For example, **Lassa virus** uses **α-dystroglycan** as its primary receptor, while others may utilize transferrin receptor 1 (TfR1) (Cao et al., 1998; Radoshitzky et al., 2007).
- Following receptor binding, viral entry occurs via **clathrin-mediated endocytosis**. Once internalized, the acidic environment of endosomes triggers a conformational change in the viral glycoprotein complex (GP), leading to **membrane fusion** and release of the viral ribonucleoprotein (RNP) complex into the cytoplasm (Quirin et al., 2008; Iheukwumere *et al*., 2025a).

2. Transcription
- The arenavirus genome consists of two single-stranded RNA segments: **L (large)** and **S (small)**, both of which are ambisense.
- Each segment encodes two proteins separated by an intergenic region forming a stable hairpin that acts as a transcription termination signal (Salvato and Shimomaye, 1989; Iheukwumere *et al*., 2025b).
- The viral RNA-dependent RNA polymerase (L protein) transcribes negative-sense portions first, producing mRNAs for **nucleoprotein (NP)** and **glycoprotein precursor (GPC)**.
- Later, after replication of antigenomes, positive-sense regions encode the **L polymerase** and **matrix protein Z** (Buchmeier et al., 2007; Iheukwumere *et al*., 2025c).
- Viral mRNAs are not capped; instead, arenaviruses employ a **cap-snatching mechanism**, stealing 5′ capped fragments from host cell mRNAs (Pinschewer et al., 2005; Iheukwumere *et al*., 2025d).

3. Translation
- Host ribosomes translate the viral mRNAs in the cytoplasm.
- The **NP** and **Z protein** are synthesized early and regulate replication. NP encapsidates viral RNA to protect it from degradation and immune recognition, while Z acts as a matrix protein and replication regulator (Cornu and de la Torre, 2001; Iheukwumere *et al*., 2025e).
- The **GPC** is synthesized as a precursor that undergoes cleavage by the cellular protease SKI-1/S1P, producing GP1 and GP2, the components of the mature glycoprotein complex responsible for receptor binding and fusion (Lenz et al., 2001).

4. Genome Replication
- Replication begins once sufficient NP has accumulated.
- The viral polymerase synthesizes full-length complementary antigenomes, which then serve as templates for producing new genomes.
- This replication process ensures the balanced production of both genomic and antigenomic RNAs for packaging (Pinschewer et al., 2005; Iheukwumere *et al*., 2025f).

5. Assembly
- Viral assembly occurs at the plasma membrane.
- The matrix protein Z plays a central role by interacting with glycoproteins, NP-RNA complexes, and the host cell budding machinery.
- Z protein contains a **late-domain motif (PPXY or PTAP)** that recruits the host ESCRT (endosomal sorting complexes required for transport) pathway, essential for virus budding (Perez et al., 2003; Iheukwumere *et al*., 2025g).

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6. Release

- New virions are released by budding from the host cell plasma membrane.
- The ESCRT machinery assists in membrane scission, enabling enveloped viral particles to exit.
- Released virions carry surface glycoproteins and contain NP-encapsidated RNA genome segments with polymerase, making them infectious for subsequent rounds of replication (Iheukwumere *et al*., 2025h).

3. Mode of transmission

Some arena virus are Zoonotic pathogens and are generally associated with rodent-transmitted disease in human. Each virus usually is associated with a particular rodent host species in which it is maintained. Arenavirus persist first and then transmitted into human.

Human can be infected through mucosal exposure to aerosols or by direct contact of abraded skin with the infections materials derived from infected rodents (Emonet *et al*., 2011). Aerosols are fine most or sprays of rodents dried excreta, especially urine that is dropped in the environment. Most of the arena viruses caught by humans and within their own homes when these rodents seek shelter. The virus can be caught in factories, from food that has been contaminated or within agricultural work areas. The risk of getting the arena virus infections for human is related to age, race, or sex within the degree of contact with dried rodent excrete. Table 1 show Arenavirus and associated diseases.

Table 1: Arenavirus that causes human disease

Virus	Disease	Year discovered
Lymphocytic Chomomentagitis virus (LCM)	Lymphocytic Choriomeningits	1933
Juin virus	Argentine hemorrhagic fever	1958
Machupo virus	Bolvian hemorrhagic fever	1963
Lassa Virus	Lassa fever	1969
Guanarito virus	Venezuelen hemorrhagic fever	1989
Sabia	Brazilian hemorrhagic fever	1993
Chapare	Chapare hemorrhagic fever	2004
Lujo	Lujo hemorrhagic fever	2008

Source: https:www.cdc.gov/about/default.htm

Pathogenesis of Arena virus

The pathogenesis of arenavirus infections involves multiple interconnected processes, including viral entry and replication, immune modulation, and tissue damage.

Viral Entry and Early Infection

The pathogenesis begins with viral entry into host cells. Arenaviruses utilize cellular receptors such as alpha-dystroglycan (α-DG) for Old World arenaviruses (e.g., *Lassa virus*) and transferrin receptor 1 (TfR1) for New World arenaviruses (e.g., *Junín* and *Machupo viruses*) (Cao et al., 2016; Iheukwumere *et al.,* 2024a). Following receptor binding, the viral envelope glycoprotein complex mediates fusion within acidic endosomes, allowing the release of viral ribonucleoproteins into the cytoplasm where replication and transcription occur. Early replication in macrophages and dendritic cells establishes initial viremia and dissemination to lymphoid and visceral tissues (Bowen and Peters, 1997; Iheukwumere *et al.,* 2024b).

Immune Modulation and Evasion

Arenaviruses have evolved mechanisms to suppress and evade host innate immunity. A key factor is the nucleoprotein (NP), which possesses an exonuclease domain that degrades double-stranded RNA, preventing recognition by RIG-I-like receptors and inhibiting type I interferon induction (Martínez-Sobrido et al., 2009). Similarly, the Z matrix protein interferes with host antiviral signaling, further dampening innate immune responses. This suppression allows uncontrolled viral replication in the early stages of infection, contributing to high viral loads and systemic spread (Iheukwumere *et al.,* 2024c).

Cytokine Dysregulation and Vascular Pathology

Disease severity is linked to immune dysregulation rather than direct cytopathic effects. In severe arenavirus infections, excessive activation of monocytes and macrophages results in the overproduction of proinflammatory cytokines such as TNF-α, IL-6, and IL-8, leading to endothelial dysfunction and increased vascular permeability (McLay et al., 2014; Iheukwumere *et al.,* 2024d). This "cytokine storm" contributes to the characteristic hemorrhagic manifestations, including mucosal bleeding, shock, and multi-organ failure. Importantly, endothelial cells themselves are rarely lysed by the virus; rather, damage arises from immune-mediated inflammation and altered vascular integrity.

Adaptive Immune Response and Immunopathology

The adaptive immune response plays a dual role in pathogenesis. In mild or asymptomatic cases, effective T-cell responses, particularly cytotoxic CD8+ T cells, contribute to viral clearance (Bruns et al., 2018; Iheukwumere *et al.,* 2024e). In contrast, in fatal cases, impaired or delayed adaptive immunity allows persistent viremia and uncontrolled immune activation. Additionally, T-cell–mediated immunopathology can exacerbate tissue damage, particularly in the liver, spleen, and vascular endothelium. Antibody responses are typically weak or delayed, limiting their protective role during acute infection.

Organ Damage and Clinical Manifestations

Arenaviruses primarily target the reticuloendothelial system, liver, and vascular endothelium. Liver involvement often leads to hepatocellular necrosis, while infection of immune cells and endothelial dysfunction result in impaired coagulation, capillary leakage, and hemorrhage (Geisbert and Jahrling, 200; Iheukwumere *et al.,* 2024f). Clinically, patients may present with fever, malaise, myalgia, and pharyngitis, progressing to hemorrhagic fever, hypotension, neurological involvement, and in severe cases, shock and death. The extent of vascular leakage and immune dysregulation determines disease outcome.

3.1 Clinical manifestation of the disease

LCM viruses cause *influenza like* febrile illness, but concessionary they may cause meningitis, characteristically

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accompanied by large number of lymphocytes in the CSF (as the name LCM suggests).

Lassa fever is characterized by high fever, severe myalgia, coagulopathy, haemorrhagic skin rash, and occasional visceral haemorrlage as well as necrosis of liver and spheen. Other Arenavirus like Junin virus muchupo virus causes heamorrhagic fever.

3.2 Distribution of the Disease

LCM virus-lassa virus (old world) complex lymphocytic choriomeningitis virus (Fig. 4).

- Rodent- *Musmusculus*and *mus*mesocriectusauratus (I.e, Syrian hamster).
- Location – Europe, Asia, and the Americans
- Habitat- perdomestric, grasslands
- Season - September to October
- Human contact - Primarily within households

Lassa virus

- Rodents *mastomys genus* (i.e, mutimummate mouse)
- Location – west Africa
- Habitat – Savana, forest clearing
- Season - January to April
- Human contact - Primarily within house

Luyo Virus

- Rodent - unknown
- Location- Zambia
- Habitat- unknown, like similar to lass virus
- Season- unknown, likely similar to lassa virus
- Humancontact- unclear, likely similar to lassa virus

Tacaribe virus (new world) complex
Junin virus (Argentine hemoeehagic fever)
Rodent - calomys*masculinus* (i.ecorn mouse) Akodonzarea (i.e, grass field mouse), *Bolomys obscures* (i.e, dark field)
Location-Aregentina
Habitat-Grasslands, cultivated fields, and hedgerows
Season- Februaryto May
Human contact- occupational in field
Machupo virus (Bolivian hemorrhagic fever)
Rodent- calomys callosus (i.e vesper mouse)
Location- Bplivia
Habitat- peridomestic, grablands
Season-April to July
Human contact- Primarily within house
Sobia virus (Brugilia hemorrhagic fever
Rodent- unknown
Location- isolated in Brazil
Human contact – single natural human infection, as well as l aboratory infections
Chapare virus
Rodents- unkown
Location- Higher altitudes near-cochabamba Bolivia
Habitat- unclear
Human contact – unclear
Guanarito virus (Venezuelan hemorrhagic fever)
Rodent- *Zygodontomys brevicauda* (I.e cane mouse)
Location – centra Venezuela
Habitat – Grass lands, brush, peridomestic
Season- November toJanuary
Human contact- within house

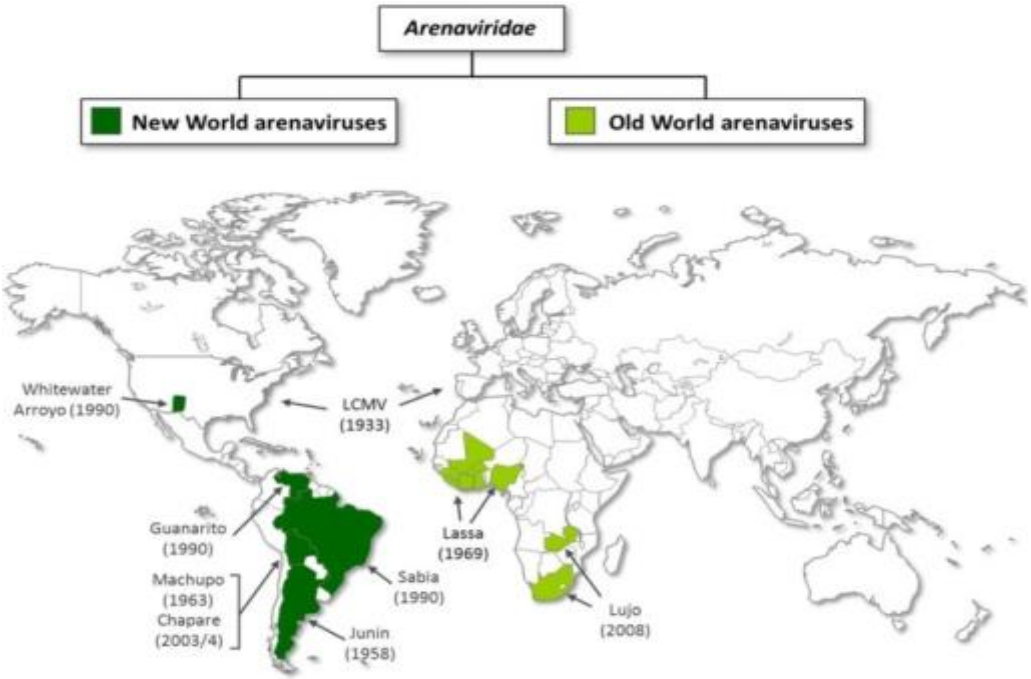

Figure 4: Geographic distribution of human pathogenic
Source: https://www.researchgate.net/publication/233828826/figure/fig5/AS:667220195676166@1536089099223/Geographic-distribution-of-human-pathogenic-arenaviruses-This-map-summarizes-the.png

4. Diagnosis

The diagnosis of acute illness with human arenavirus is made using antigen and/or antibody measurements, virus isolation, and or genomic detection by reverse transcriptase–polymerase chain reaction (RT PCR). For Lassa and the South American hemorrhagic fever agents, laboratory samples from suspended cases should be handed under biosafety level 4 containment until treated chemically (10% hypochlorite, Lysol, formaldehyde, or peracetic acid) or with gamma irradiation (Emonent et al., 2011).

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Antigen-antibody detection
The serodiagnosis of Arenavirus can be made rapidly and with a high degree of sensitivity.

In lassa fever, many acutely ill patients can be found to be immunoglobin m (lgm) antibody positive for the lassa virus upon presentation. Indirect fluorescent antibody (IFA) assay or enzyme-linked immunoabsorbent assay (ELISA) methodology usually determines the lgm antibody. At least 50-75% of patients are lgmantibody positive (i.e, ≥ 1:4) byday 5 and 100% positive by days 12-14 (Hass et al., 2016).

Virus isolation
Lassa virus can be isolated easily (i.e., in a biosafety level 4 containment laboratory) in tissue culture using ∑ 6 clones of Vero cells or in suckling mice.
In human infection with LCM virus, the virus can be isolated from the blood early in the disease, and in those who develop meningitis, the virus also can be isolated later from CSF (CDC, 2014).

Reverse transcriptase polymerase chain reaction detection Limited experience exists with RT-PCR. Care must be taken to avoid false-positive results and to use appropriate primers.
RT-PCR assays detecting fragments of the s (glycoprotein) gene have been successful, and, after RNA extraction minimal laboratory risk exists.

4.1 Treatment
This virus can be very devastating yet there are very few treatment methods available. The only licenced drug for the treatment of human Arenavirus infection is the nucleoside analogue ribavirin (Lee et al., 2011). Ribavirin reduces morbidity and mortality in humans who have certain Arenavirus, such as LASV and JUNV infections, if it is taken in the early stages of the disease, Ribavirin displays mixed success in treating severe Arena viral disease and is associated with significant toxicities (Mendenhall *et al*.,2010). Effective antiviral drugs need to be produced at low cost, taken orally, and to withstand tropical climates due to the regions where these infections are occurring.

4.2 Prevention
Recognition of a case of Lassa fever or any other South American Arenavirus infection is crucial from both infection control and epidemiologic standpoints. Suspected cases should be reported immediately to local public health authorities (Briese *et al*., 2009).

Rodent Control
Unlike plague, in which a rodent die-off can cause an increased risk of a human out beak, the rodents carrying arenaviruses do not become ill in shed the illness in their urine.
Aggressive rodent control (eg, trapping, rodent poisons) and avoidance of high- density rodents areas are the most important preventative maneuver.

Nosocomical Spread Prevention
Person-to-person spread has been problematic within hospitals where lassa fever is endemic (Hass et al., 2016).

Patients should be placed in a single room with isolated should be placed in a single room with isolated negative pressure airflow. Isolation should be continued until multiple blood or urine specimens are negative for the virus. All tests with arena virus should be conducted in special laboratories with BSL4 containment.

Arena Virus Vaccination
No commercially available vaccines are available to prevent arena virus that expressed lassa virus glycoprotein was found to be efficacious in primates (Botten et al., 2012). Field trails with an attenuated junin virus vaccine have shown an efficacy of 95% with minimal slide effects.

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