South American Hemorrhagic Fevers

A Quick Review

Gaby Frank, MD, FACP, SFHM

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JOHNS HOPKINS
MEDICINE

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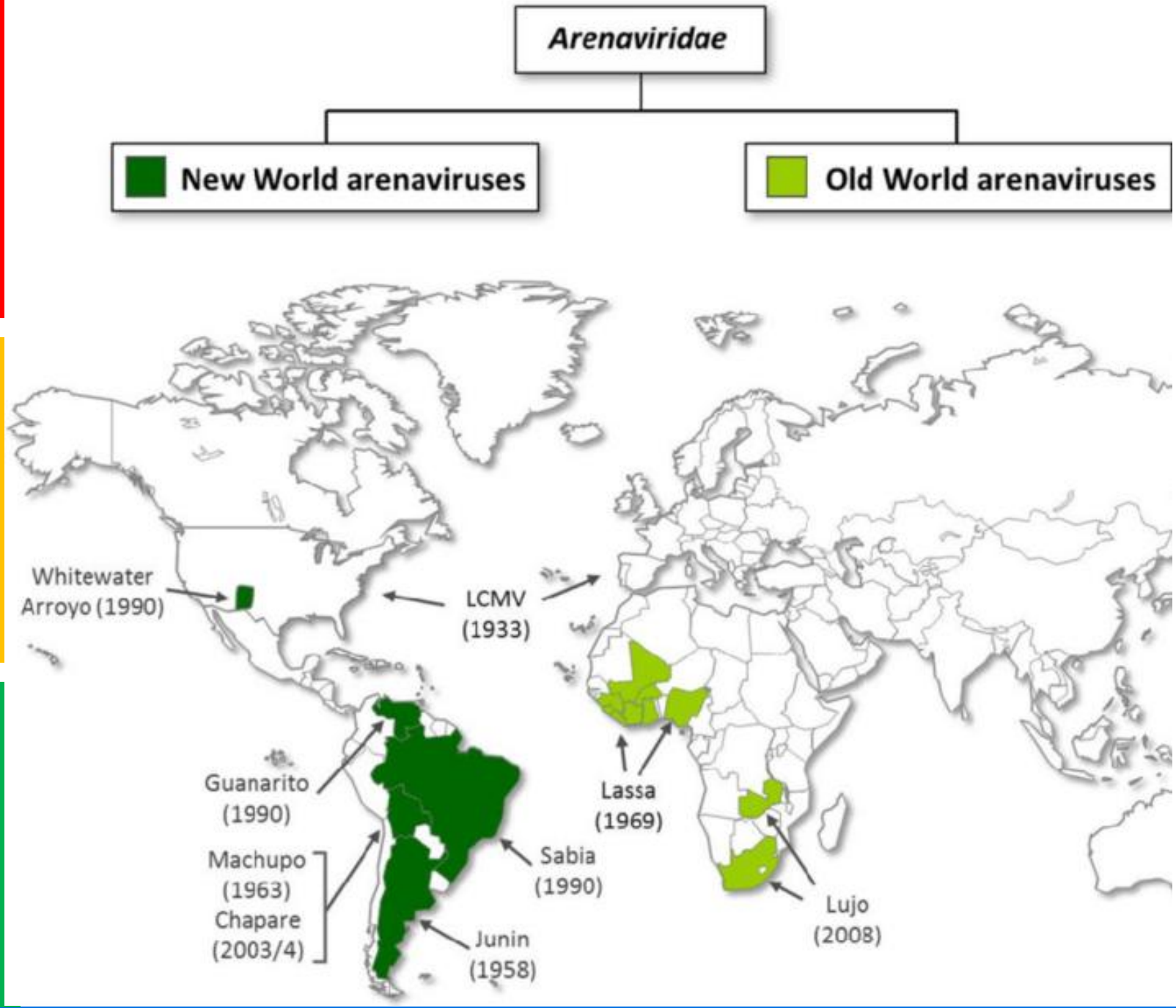
South American Hemorrhagic Fevers (SAHF) are a group of zoonotic viral infections present in South America, which have the potential to cause severe illness leading to organ dysfunction, bleeding, and death.

Caused by Arenaviruses, enveloped, ambisense (or is it?), segmented, single stranded RNA viruses

The Old and the New



Clade B NW Arenaviruses

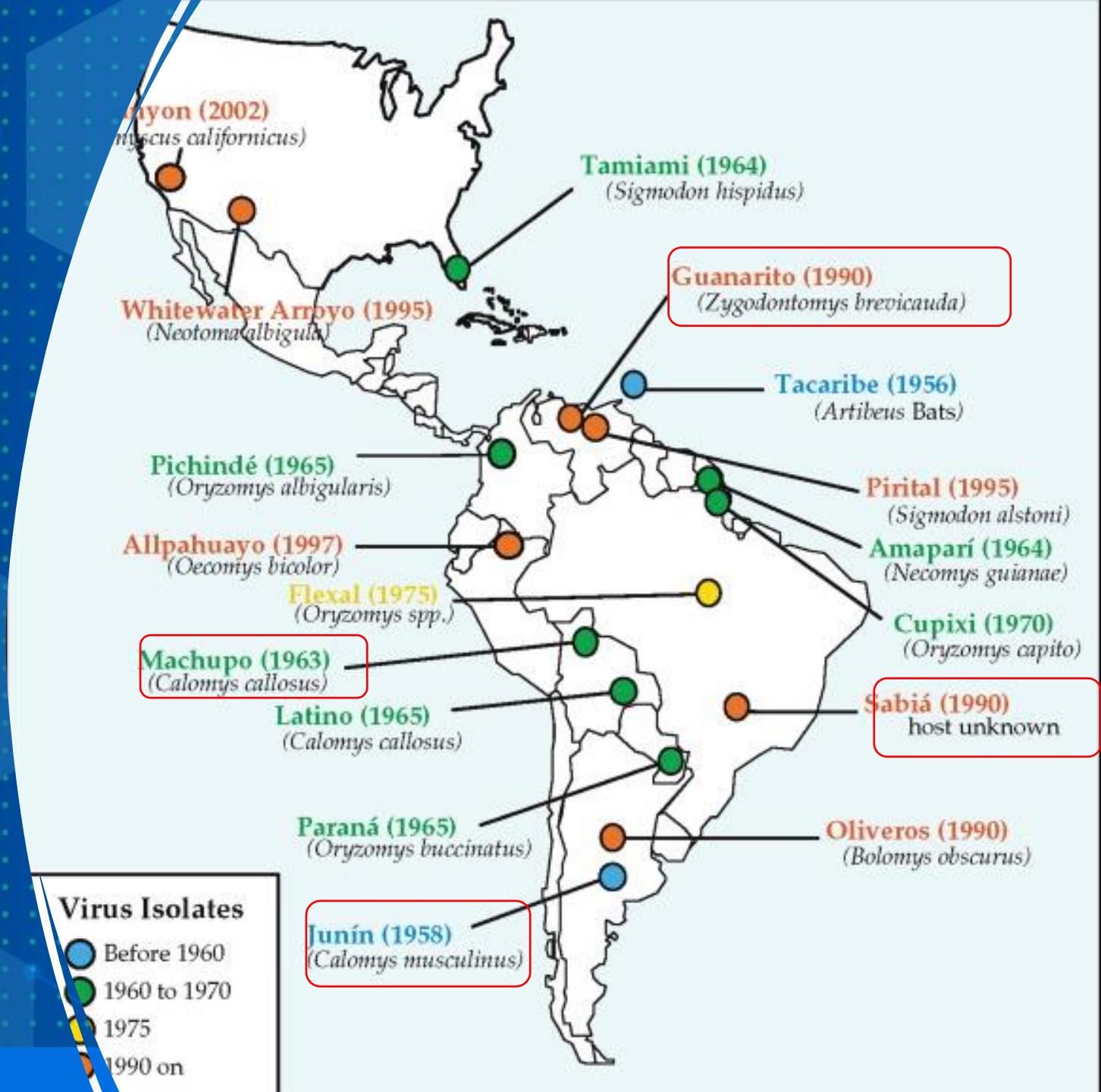
New World Arenavirus	Country	Reservoir	Described Infections in Humans
Junín virus	Argentina	Calomys musculinus, Calomys laucha, Akodon azarae, Orizomys flavescens	Yes- First isolated in 1958
Chaparé virus	Bolivia	Unknown	Yes- First isolated in 1960
Machupo virus	Bolivia	Calomys callosus	Yes- First isolated in 1963
Tacaribe virus	Venezuela	Artibeus jamaicensis (bat)	Febrile, non-fatal laboratory acquired infections
Guanarito virus	Venezuela	Zygodontomys brevicauda	Yes- First recognized in 1989
Sabiá virus	Brazil	Unknown	Yes- First isolated in 1990
Amapari virus	Brazil	Neacomys guianae	Not yet described
Cupixi virus	Unknown	Unknown	Not yet described

Epidemiology

Junin virus- Argentina

Machupo virus- Bolivia

Guanarito virus- Venezuela



Transmission

- Zoonosis: contact with infected rodents and their environment
  - Person-to-person (Junin, Chapare, Machupo, Lassa, Lujo) Household and nosocomial
    - Laboratory acquired
    - Sexual transmission

New World Arenavirus- Clade B- Distribution and Reservoir.

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Clinical phases

Incubation (3-21 days)

Acute 1st week
Acute 2nd week

Convalescence

Clinical Presentation

- Epidemiologic Exposure
- Clinical Spectrum
- Special populations
- Late Neurologic Syndrome

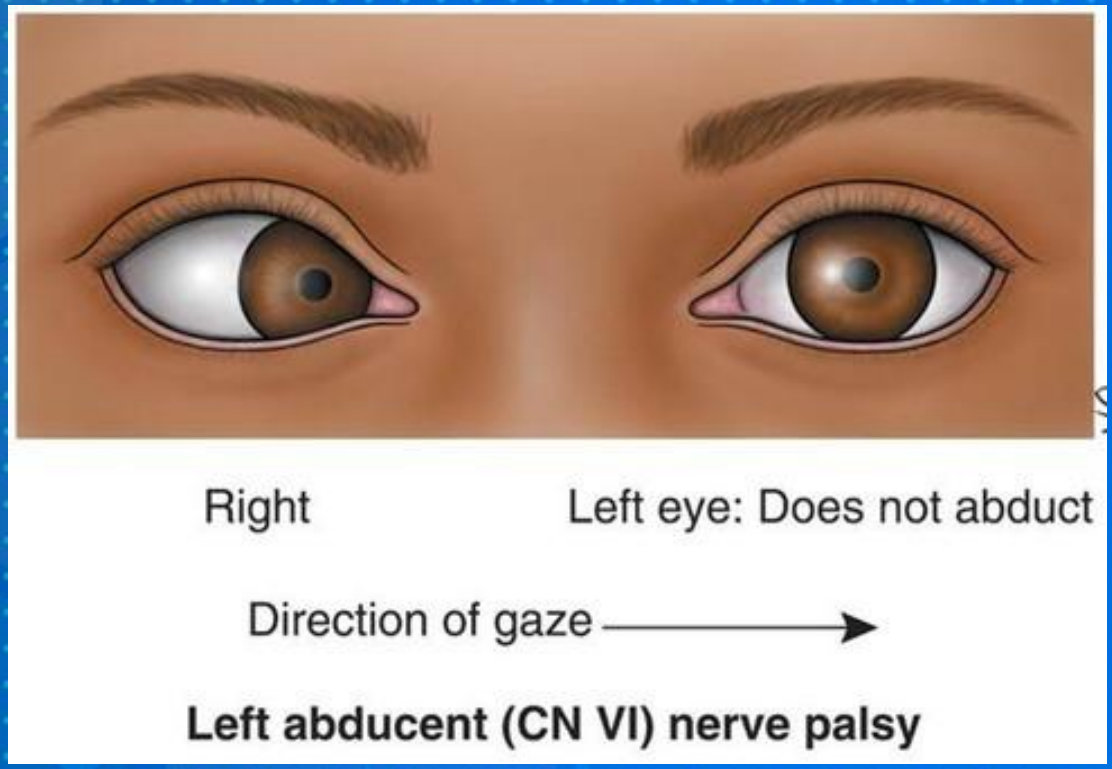
more

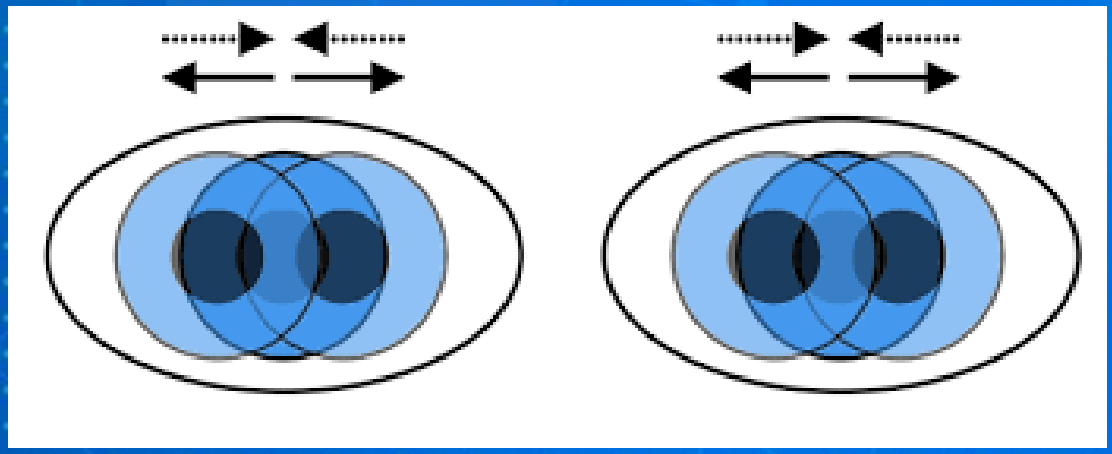
Clinical presentation of South American Hemorrhagic Fevers (SAHF).

Hemorrhagic Fever	Arenavirus	Geographic distribution	Incubation	Early clinical manifestations	Late Clinical manifestations	Mortality
Argentine Hemorrhagic Fever	Junín Virus	Argentina, Buenos Aires, Santa Fe, La Pampa, and Córdoba provinces	6–14 days	Flu-like syndrome. Lack of respiratory symptoms is cardinal	Late Neurological syndrome (LNS)	15%–30% <1% with treatment
Bolivian Hemorrhagic Fever	Machupo Virus	Bolivia, Itenez province	3–16 days	Flu-like syndrome. One-third of cases may progress to progressive neurological and hemorrhagic syndrome	None reported	25%
	Chaparé virus	Bolivia, Cochabamba (small outbreak late 2003, 1 fatality)	3–16 days	Flu-like syndrome Gastrointestinal bleed May progress to ARDS and multiorgan failure.	None reported	60%
Venezuelan Hemorrhagic fever	Guanarito virus	Venezuela, Portuguesa and Barinas state	Up to 19 days	Flu-like syndrome. May present with Upper Respiratory symptoms. May progress to progressive neurological and hemorrhagical syndrome.	None reported	33%
Brazilian Hemorrhagic Fever	Sabiá virus	Brazil, Sao Paulo	6–21 days	Flu-like syndrome, may progress to multiorgan failure	None reported	50%

LNS- AHF

- **10% pts** s/p JUNV CP (>8 days from the onset of illness)
  - dizziness,
  - headache, and
  - nausea after recovery.
- After symptom-free for a period LNS patients develop
  - fever
  - cranial nerve palsies (VI most common 60% of pts) and
  - cerebellar deficits (nystagmus in up to 50% of pts)
- Almost **two-thirds of LNS** patients develop
  - tinnitus,
  - blurred vision,
  - gait ataxia within 7 days
  - 40% diplopia
  - <10 % hypo or hyperreflexia, extrapyramidal signs, or paresis
- **CSF of LNS**
  - lymphocyte-predominant,
  - normal glucose and protein,
  - antibody titers to JUNV higher than those in serum(suggesting immune-mediated mechanism)
- Symptoms are transient (few days- several months)





Mortality Risk factors

- Development of hemorrhagic features
- Development of neurological symptoms
- Shock with multiorgan failure
- Sepsis and bacterial superinfection
- Elevated TNF-a, IL-6, IL-8, IL-10, C-GSF, and thrombopoetin levels (Marta et al., 2000)
- Marked thrombocytopenia and leukopenia (Shao et al., 2015)

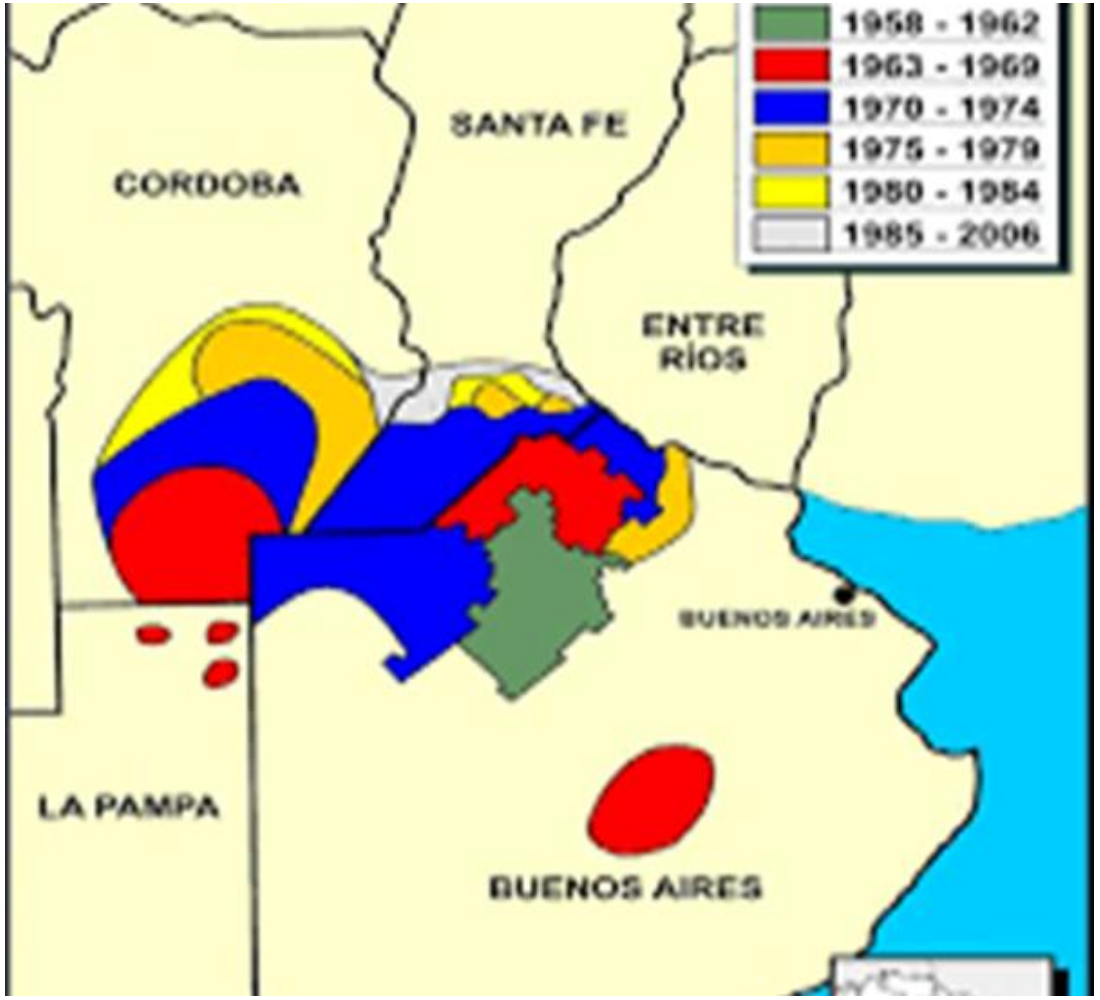
Probable case: an acute febrile illness in a patient with possible exposure to AHF endemic area and to field rodents within the previous 3 weeks

Confirmed case: a clinical case as described above, plus a laboratory confirmation of JUNV infection, either by the isolation of the virus or seroconversion

In endemic areas: the combination of

- thrombocytopenia <100K and
- leukopenia WBC < 4K

has a sensitivity of 100% and a specificity of 71% for AHF



Human Vaccines 7:6, 1-7; June 2011; © 2011 Landes Bioscience

DIAGNOSIS

ACUTE PHASE	CONVALESCENCE	DECEASED
Sample obtained before CP	Sample obtained 60 days after symptom resolution	At any time after death, may use any bodily fluid or tissue
Serum, blood, urine		
Viral detection: RT-PCR	Serum Elisa IgG, PRNT	Viral detection: RT-C-PCR, IHC Immune Response: Elisa, PRNT
Immune resp.: Elisa IgG, PRNT		

Laboratory Testing

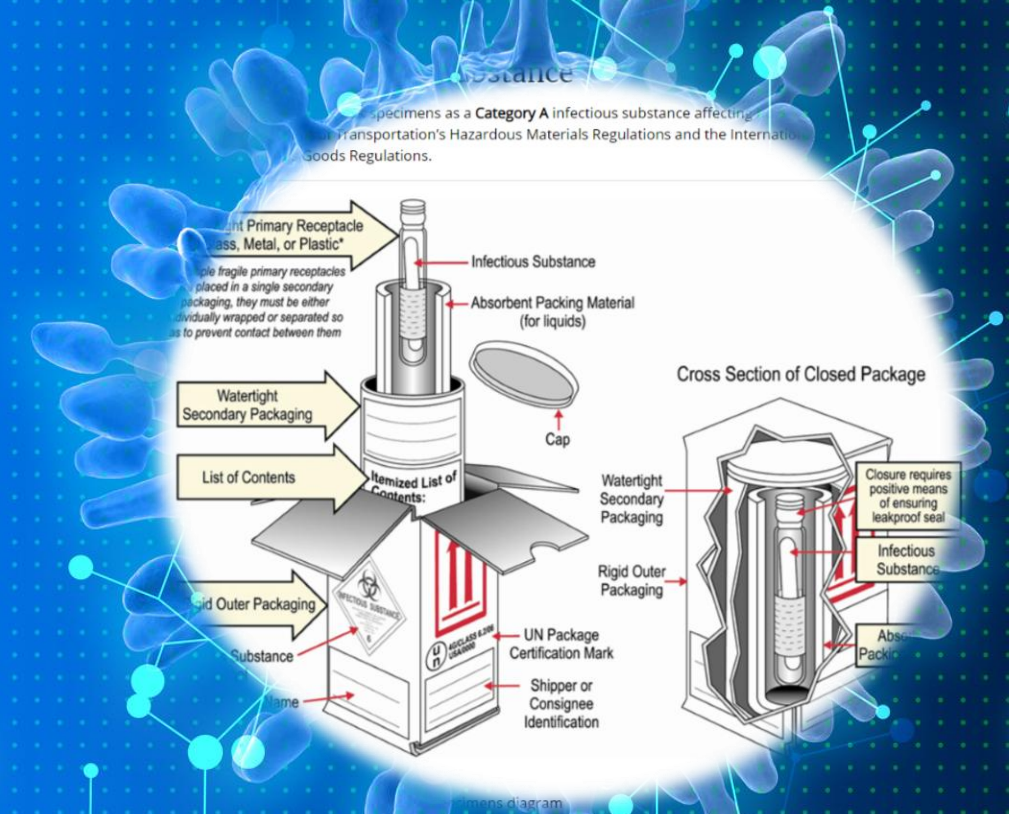
Testing is not available at RESPTCs

Must submit testing to CDC in Atlanta. (USARMRIID*)

Must have consultation with CDC prior to submission.

Must report to PH and gain approval prior to submission.

Category A infectious substance: only packaged by those with training (HRP lab staff, Micro staff)



Clinical Management

- Supportive therapy
- Antivirals (off-label)
  - Ribavirin (Guanosine analog)
  - Favipiravir (viral RNA polymerase inhibitor)
- Convalescent Plasma (JUNV)
  - Mortality from 16.6 to 1.1 %
  - Late administration increases risk for LNS
- Monoclonal Abs (anti-hTfR1), not commercially available

TREATMENT

The specific treatment available for AHF is **IMMUNE PLASMA**

Administered during the first 8 days from the onset of symptoms reduces lethality from 15-30% to around 1%.

It is obtained from individuals who suffered from the disease and recovered.

DOSIS: 3500 TU/ Kg.

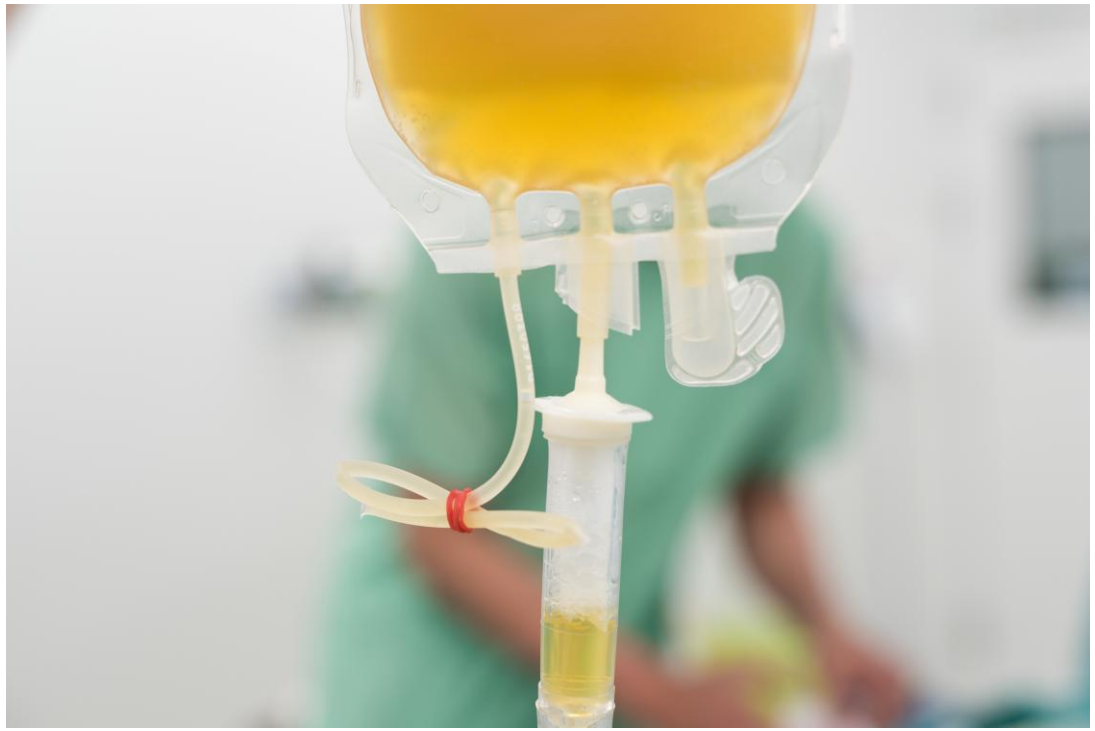


Image credit: https://www.nursingcenter.com/blogs-plus/blogs/blogs-post?identifier=Convalescent-Plasma-Therapy-Is-it-a-Viable-Treatme#/post/Convalescent-Plasma-Therapy-Is-it-a-Viable-Treatment

Pre-Exposure Prophylaxis

GENERAL MEASURES

- Individual (washing hands, boots, gloves).
- Environmental.
- Rodent control.

SPECIFIC MEASURES

- **Vaccine Candid#1**

Vaccination against Argentine Hemorrhagic Fever (AHF) is recommended from the age of 15 for individuals residing or traveling in the endemic areas of the disease in the provinces of Santa Fe, Córdoba, Buenos Aires, and La Pampa. Vaccination should be carried out at least one month before engaging in risky activities to ensure protection.

Pre-Exposure Prophylaxis

https://sintinta.com.ar/2021/09/21/argentina-vuelve-a-producir-una-vacuna-discontinuada-en-2018/

- CANDID #1: a live attenuated virus vaccine for the prevention of AHF, was developed jointly by the Argentine Ministry of Health and Social Action and the U.S. Army Medical Research Institute of Infectious Diseases.
- The vaccine became available in 1991 and is only licensed for use in Argentina.
- JUNV is the only SAHF virus for which preventative vaccination is available

Postexposure prophylaxis

- **No data**
- Ribavirin, favipiravir
- Passive immunization
- Immunomodulatory agents

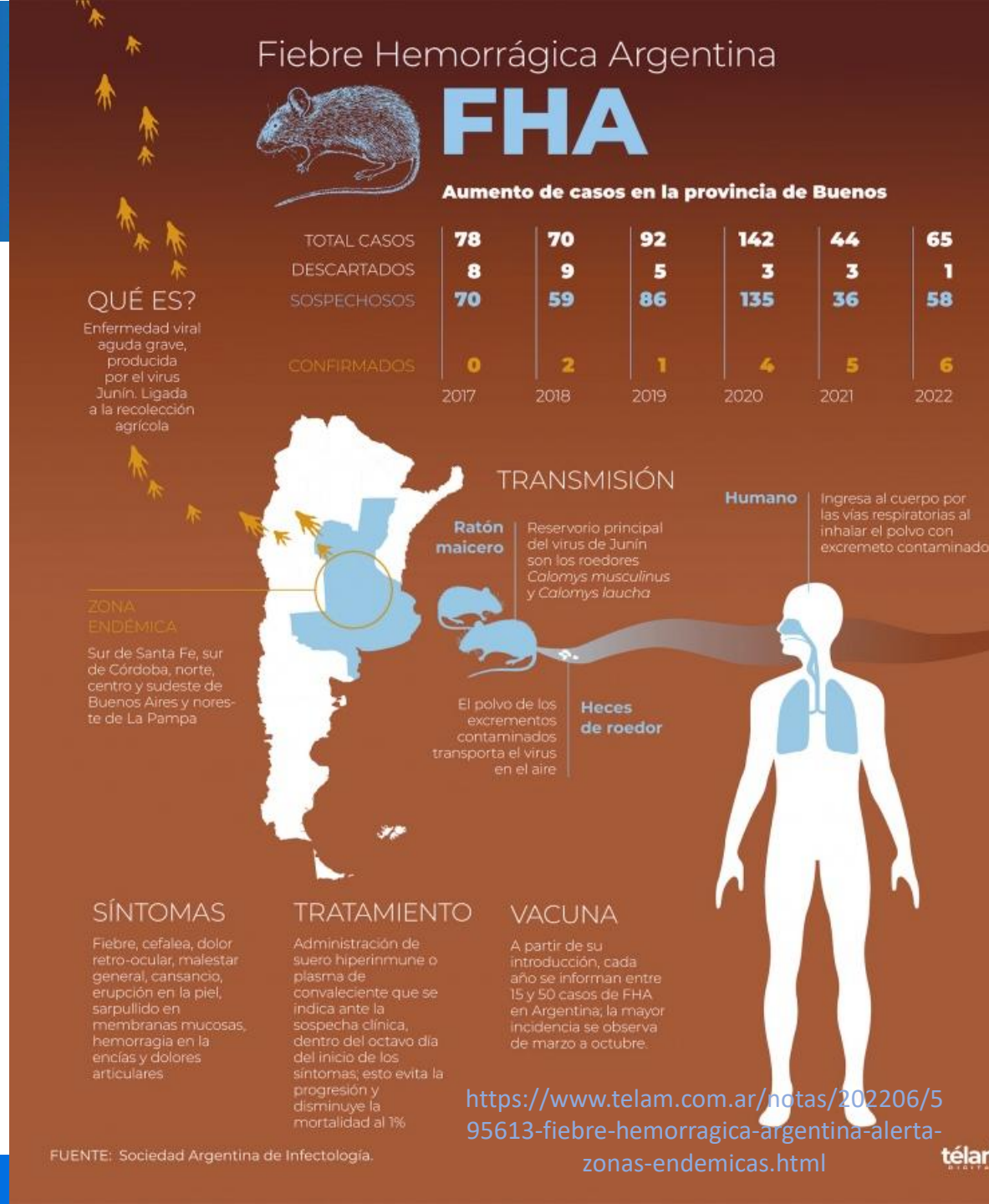
Category A PPE – PAPR with double shroud, 3 layers of gloves, impermeable suit, booties.
Category A waste
Negative pressure room

Potential for high severity
Potential to cause large-scale outbreaks
Potential to cause nosocomial infection in hospital or field setting
Scarcity of available MCM

Differential Diagnosis

Epi Hx: residence, occupation, travel, food storage, animal exposure, sick contacts, etc. within last 3 weeks

- Influenza, other URIs
- Typhoid
- Brucellosis
- Q Fever
- Rickettsiosis
- Ehrlichiosis
- Lyme
- Leptospirosis
- Salmonellosis
- Tick-borne encephalitis
- Malaria
- Lassa fever
- Rift Valley Fever, Hantavirus disease
- Marburg and Ebola
- Yellow Fever, Dengue, Kyasanur Forest disease, Omsk HF, Al Khumrah



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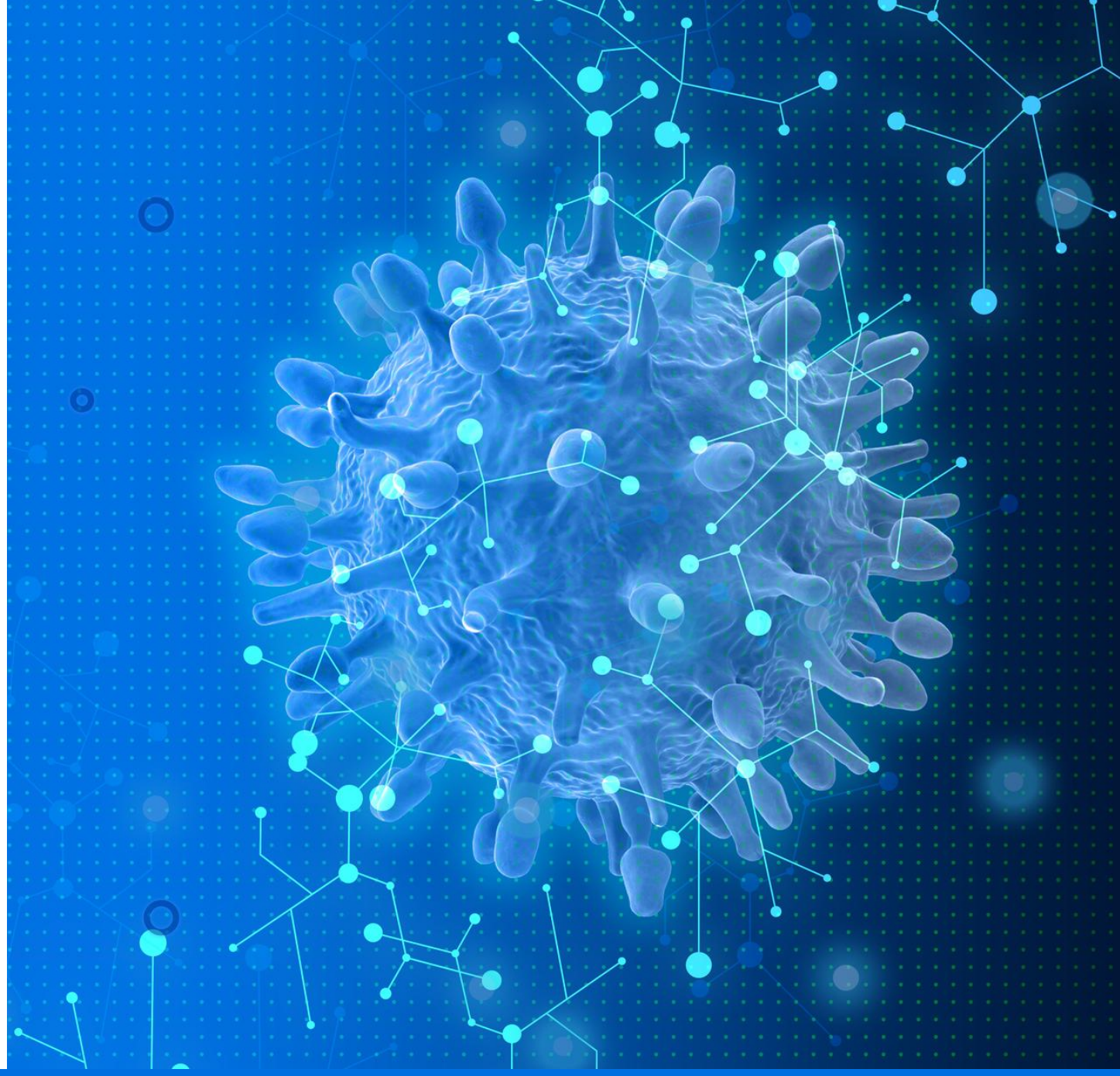

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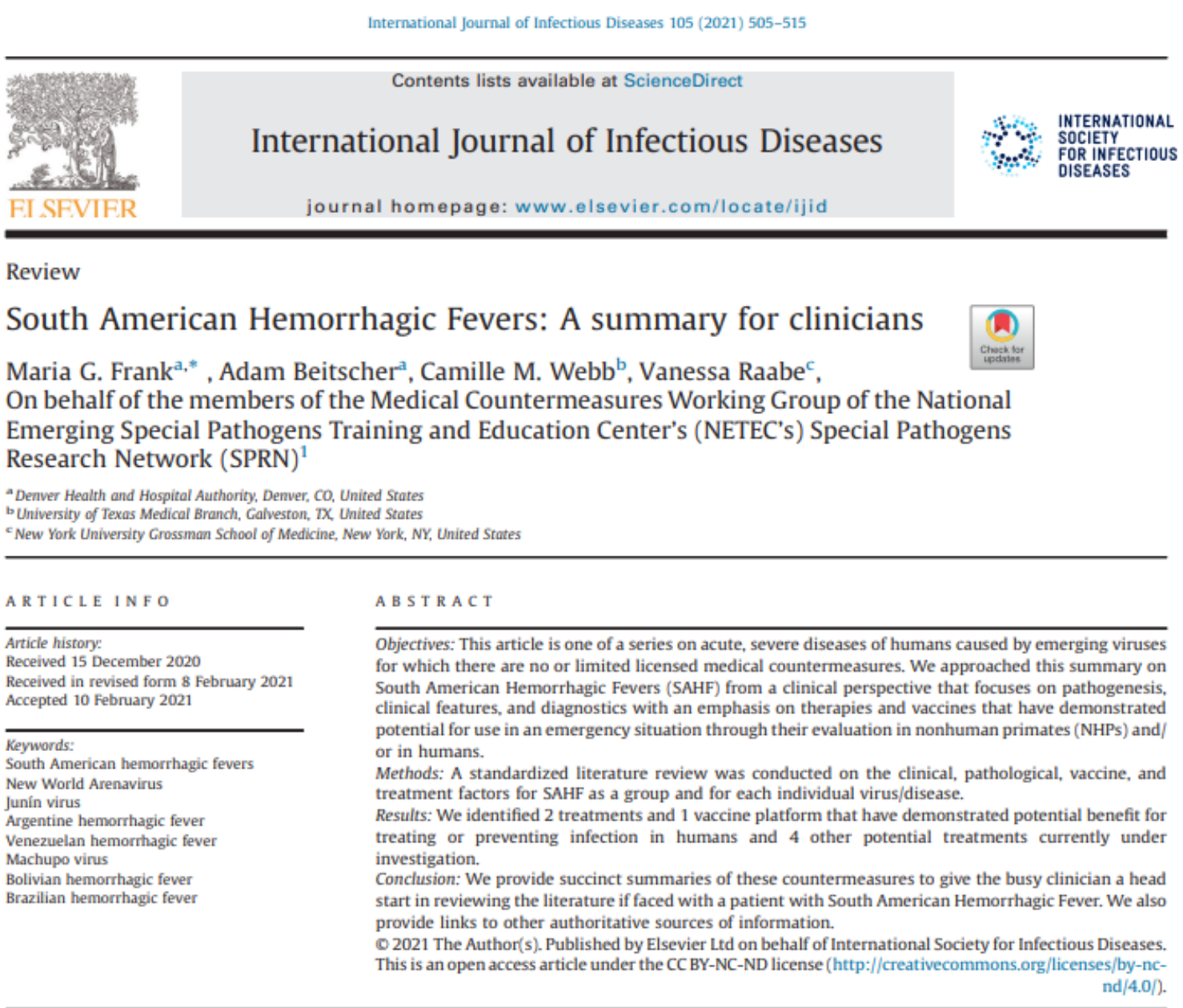

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Review

South American Hemorrhagic Fevers: A summary for clinicians

Maria G. Frank[a,*], Adam Beitscher[a], Camille M. Webb[b], Vanessa Raabe[c], On behalf of the members of the Medical Countermeasures Working Group of the National Emerging Special Pathogens Training and Education Center's (NETEC's) Special Pathogens Research Network (SPRN)[1]

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Brazilian hemorrhagic fever

ABSTRACT

Objectives: This article is one of a series on acute, severe diseases of humans caused by emerging viruses for which there are no or limited licensed medical countermeasures. We approached this summary on South American Hemorrhagic Fevers (SAHF) from a clinical perspective that focuses on pathogenesis, clinical features, and diagnostics with an emphasis on therapies and vaccines that have demonstrated potential for use in an emergency situation through their evaluation in nonhuman primates (NHPs) and/or in humans.
Methods: A standardized literature review was conducted on the clinical, pathological, vaccine, and treatment factors for SAHF as a group and for each individual virus/disease.
Results: We identified 2 treatments and 1 vaccine platform that have demonstrated potential benefit for treating or preventing infection in humans and 4 other potential treatments currently under investigation.
Conclusion: We provide succinct summaries of these countermeasures to give the busy clinician a head start in reviewing the literature if faced with a patient with South American Hemorrhagic Fever. We also provide links to other authoritative sources of information.

Additional Resources

Maria G. Frank, Adam Beitscher, Camille M. Webb, Vanessa Raabe. South American Hemorrhagic Fevers: A summary for clinicians. https://doi.org/10.1016/j.ijid.2021.0 2.046

https://www.cdc.gov/viral-hemorrhagic-fevers/about/?CDC_AAref_Val=https://www.cdc.gov/vhf/virus-families/arenaviridae.html

Clinical presentation of South American Hemorrhagic Fevers (SAHF).

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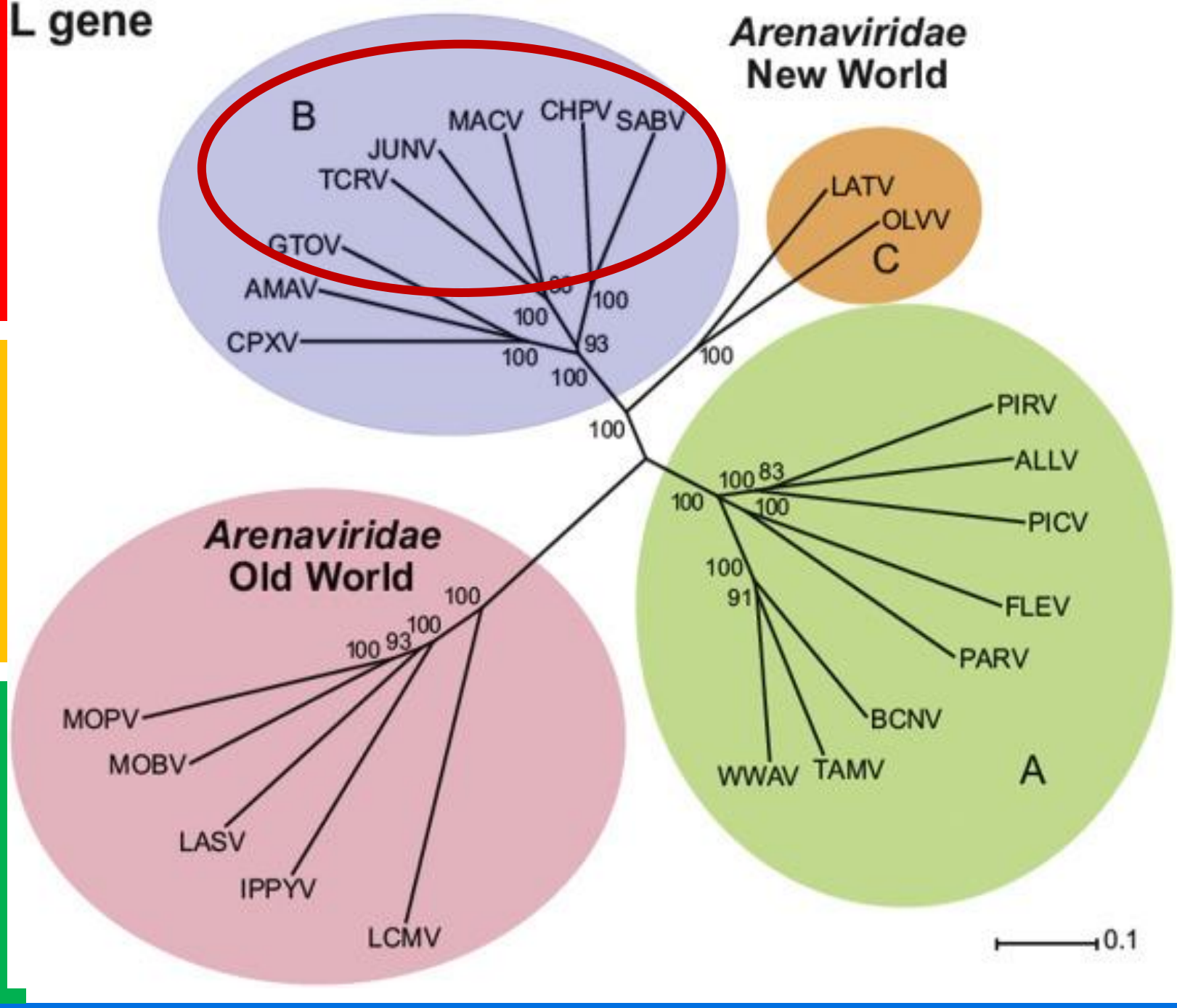
Brazilian Hemorrhagic Fever	Sabiá virus	Brazil, Sao Paulo	6–21 days	Flu-like syndrome, may progress to multiorgan failure	None reported	50%

Arenaviridae

Old World
- Lassa
- Lujo
- LCMV

New World
- Junin
- Chapare
- Sabia
- Guanarito
- Machupo



https://doi.org/10.1016/B978-0-12-800946-8.00023-4

Common clinical features of SAHF	Argentine HF	Venezuelan HF	Bolivian HF	Brazilian HF^
Signs and Symptoms				
Fever	97%	92.7%	>90%	100%
Malaise	74%	74.5%	+++	100%
Headache	58%	58.2%	+++	100%
Myalgia	54% ,LBP 64%	31%	+++	100%
Arthralgia	52%	53%	Not reported	Not reported
Oral enanthem	87%	*	*	*
Odynophagia	Not described	36.5% (Tonsillar exudates 13%)	*	33%
Cough	Not described	20%	Not described	Not described
Nausea	45%	13%	+++	100%
Vomiting	34%	34%	++	70%
Diarrhea	27%	27%	+	*
Abdominal Pain	30%	31%	++	*
Gingival bleeding	12%	53%	+++	100%
Dehydration	30%	30%	+	33% (leading to MOF)
Hemorrhagic symptoms (GI tract, GU track)	20-30% (2^{nd} week)	-Melena: 20% -Hematemesis: 16.4% -Rectal bleeding: 9%	+ (one third of patients)	-Metrorrhagia 33% -Hematemesis 33%
Seizures	18% (2^{nd} week, poor prognosis)	18.2%	+	33%
Neurologic symptoms	- 16% Tremors - progressive	Approximately one third	+ (one third of patients)	Approximately one third

Common clinical features of SAHF	Argentine HF	Venezuelan HF	Bolivian HF	Brazilian HF^
Physical exam findings				
Petechial rash	60% (common in axilla, soft palate, gingival margin in 1st week)	16%	++	33% (conjunctival petechiae)
Lymphadenopathies	87% (cervical)	24%	++	66% (cervical)
Hepatomegaly	Not common	6%	*	
Splenomegaly	Not common	2%	*	
Conjunctival congestion/ peri-orbital edema	90.3%	15%	++	Not described

Common clinical features of SAHF	Argentine HF	Venezuelan HF	Bolivian HF	Brazilian HF^
Laboratory Findings				
Thrombocytopenia <100,000/mm³	100%	100%	100%	66%
Leukopenia <4000/mm³	87%	85.7%	100%	66%
Proteinuria >1 g/L	42%	Not described	++	33%
Other				
Late neurologic Syndrome	10% of cases treated with Junín virus immune plasma	Not described	Not described	Not described
Mortality	15-30% (<1% with treatment)	33%	6-15%	33%

Special Populations

AHF during pregnancy has been infrequently reported; however, mortality of near 50% presenting during the third trimester.

Fetal and neonatal deaths as well as congenital malformations have been reported in association with JUNV infection during pregnancy.

Most children with AHF appear to have mild disease

ARGENTINE HEMORRHAGIC FEVER - AHF

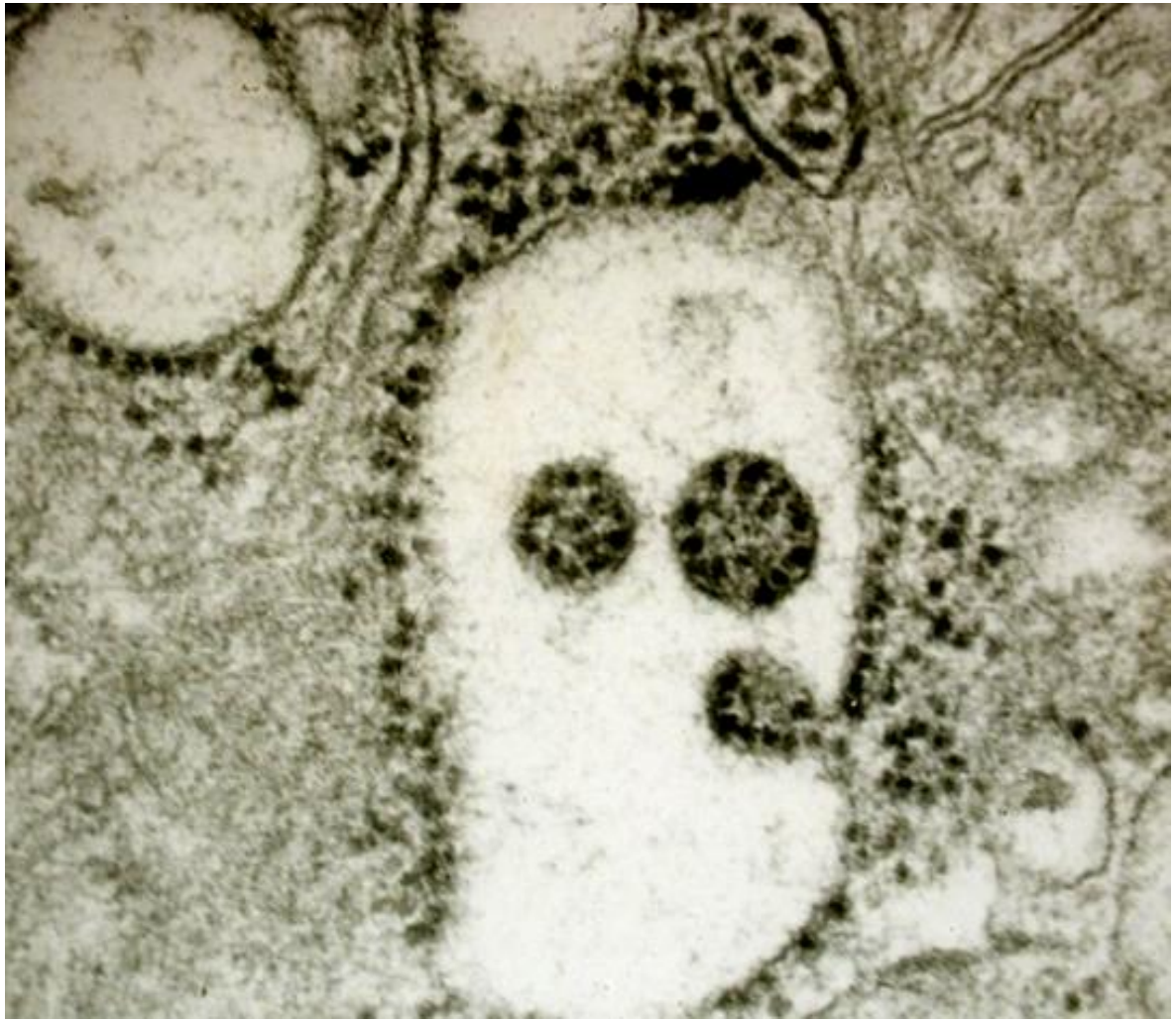
In the 1950s, a new disease was recognized in the most important agricultural region of Argentina.

Due to its clinical manifestations, it was called Argentine Hemorrhagic Fever (AHF).

The initial case fatality rate was 30 - 50%.

Since then, annual outbreaks have been recorded without interruption and with a progressive geographical extension of the endemic area.

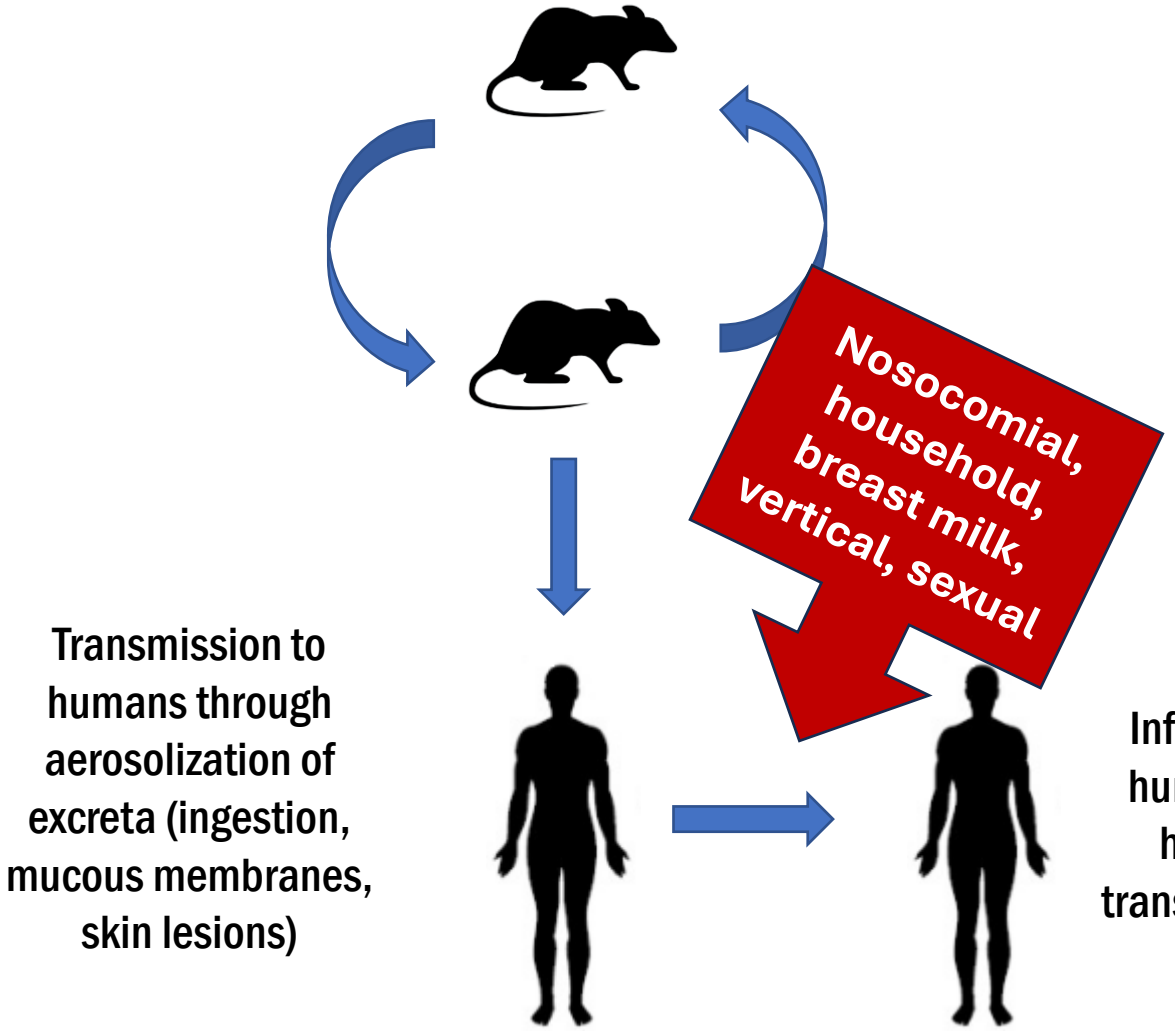
In 1958, its etiological agent was identified, which was called the **Junín virus.**



AHF – TRANSMISSION CYCLE

RESERVOIR
Calomys musculinus

Develops chronic infections
Eliminates viruses through saliva, urine and fecal matter.



Transmission to humans through aerosolization of excreta (ingestion, mucous membranes, skin lesions)

Infrequent human-to-human transmission.

AHF - EPIDEMIOLOGY

The classic epidemiological pattern has been the highest occurrence of cases in **rural male workers (80%)** between 15 and 65 years of age.



The impact of vaccination of the male population exposed to higher risk significantly decreased the incidence of the disease and generated changes in risk patterns.

ACUTE PERIOD – 1st WEEK

No evidence of respiratory compromise such as: Productive cough Odynophagia Nasal congestion Rhinorrhea

Disease begins insidiously :

Fever - Chills - Fatigue - Anorexia- Headache - Myalgia

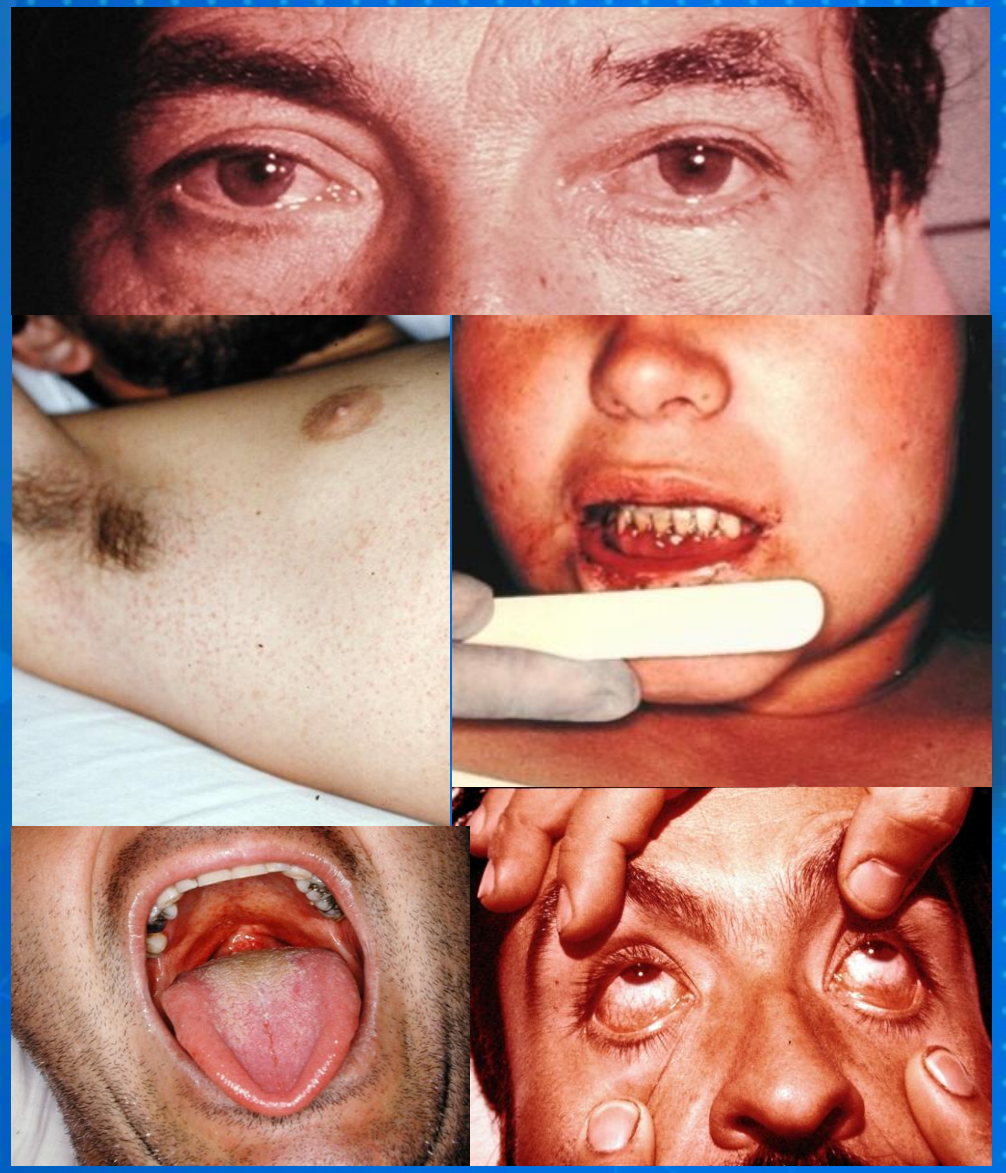
And progressively :

- Arthralgia- Retro-ocular pain
- Abdominal and lumbar pain
- Dizziness
- Nausea and/or vomiting - Diarrhea or constipation.
- Epistaxis and/or discrete gingivorrhagia.
- Metrorrhagia
- Dehydration

ACUTE PERIOD – 1st WEEK

PHYSICAL EXAM:

- Erythematous rash on face, neck and upper trunk.
- Isolated petechiae or in the form of small bouquets on the skin of the axillary regions or on the inner surface of the upper third of the arms.
- Conjunctival injection and periorbital edema. Diffuse congestion of the nasal and oral mucosa. Gingival edge. Spontaneous gingivorrhages or epistaxis.
- Dry or coated tongue. Oropharyngeal enanthem characterized by an increase in the vascular network of the soft palate and pharynx, with petechiae and micro-vesicles.



ACUTE PERIOD – 1st WEEK

NEUROLOGICAL SIGNS (end of the 1st week):

Irritability – Drowsiness – Slowness in responses – Fine tremor of hands and tongue – Moderate ataxia – Cutaneous hyperesthesia – Muscular hypotonia –hyporeflexia

BLOOD

- Leukopenia: By the end of the 1st week values between 1,200 to 2,000/mm3
- Thrombocytopenia: End of the 1st week values between 60,000 to 80,000 /mm3
- ESR: normal or decreased

URINE

- Albuminuria
- Sediment: hyaline and granular cylinders and round cells with cytoplasmic inclusions called viral-type cells.

ACUTE PERIOD – 2nd WEEK

70-80% of patients begin to improve.

20-30% evolve to severe forms of the disease, adding severe hemorrhagic and/or neurological manifestations, shock and superimposed bacterial infections.

Severe forms, whether hemorrhagic, neurological or mixed, are fatal in 90% of cases.

ACUTE PERIOD – 2nd WEEK

HEMORRHAGIC SYMPTOMS

- Hematemesis
- Melena
- Hemoptysis
- Epistaxis
- Ecchymosis
- Hematomas
- Metrorrhagia
- Hematuria

NEUROLOGIC SYMPTOMS

- Sleep disturbances
- Fine muscle tremors
- Confusion
- Psychomotor Agitation
- Stupor
- Seizures
- Coma

CONVALESCENCE

Most patients who recover show improvement by the third week of evolution.

The duration of convalescence is variable, lasting up to 1-2 months for complete recovery.

Common symptoms include:

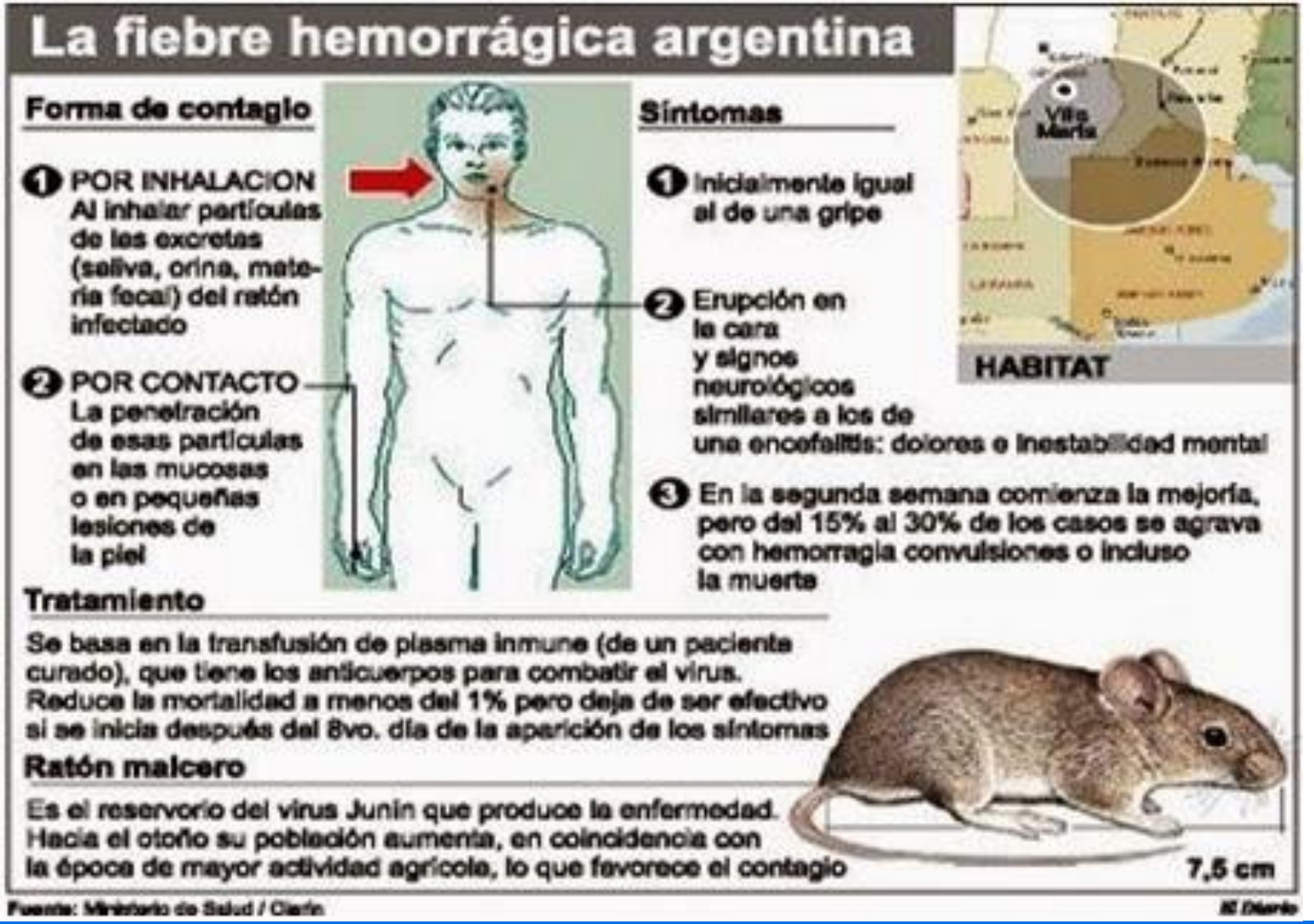
- Hair loss
- Asthenia
- Irritability
- Hearing loss
- Changes in memory

During convalescence, 10% of patients treated with Immune Plasma may develop - after a disease-free period of approximately 3 or 4 weeks - a **Late Neurological Syndrome (LNS).** AKA *"Relapse"*.

These symptoms are transient and gradually disappear.

Diagnosis

- Immunohistochemistry,
- Viral culture, and
- RT-PCR can be performed to identify the causative agent from samples such as blood or tissue
- Seroconversion
- THINK DDx!!!!!



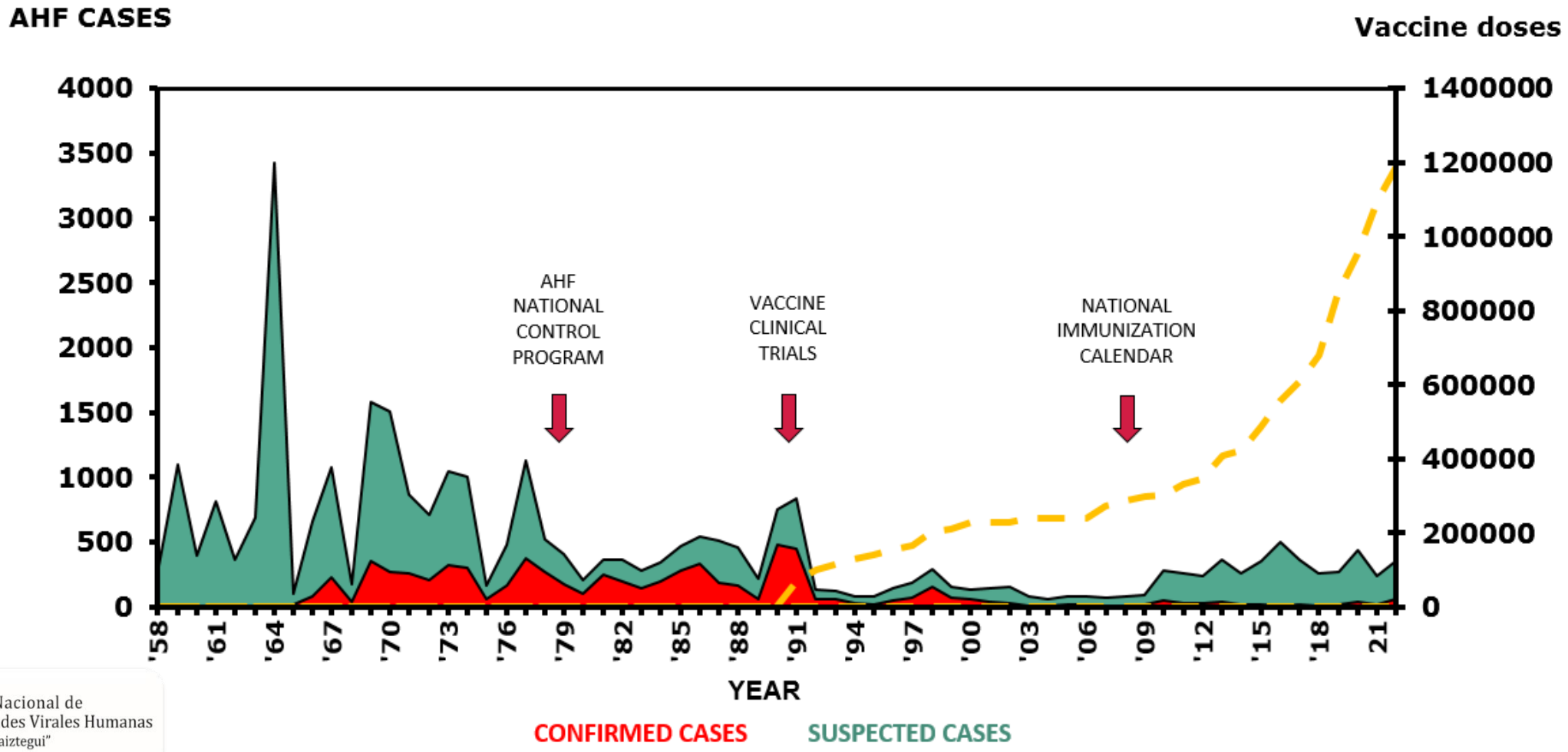
http://noticeptn26lalimpia.blogspot.com/2015/04/un-gran-doctor-entre-nosotros.html

Specimen options

1) **PCR/Virus Isolation**: lavender/blue/yellow top whole blood. Frozen on dry ice.
2) **Serology:** whole blood or serum, less than 4C
3) **Immunohistochemistry (IHC):** Tissues – preferred are lung, kidney, spleen. Alternatives: lymph nodes, heart, pancreas, pituitary, brain or liver. Preferred paraffin block. Formalin fixed tissue slides at room temp ok.

Approx. TAT: 5 days

AHF – CASE DISTRIBUTION 1958 - 2022



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