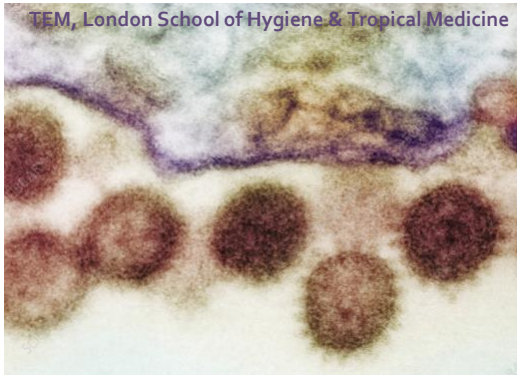
CCHF diagnosis, a challenge ?



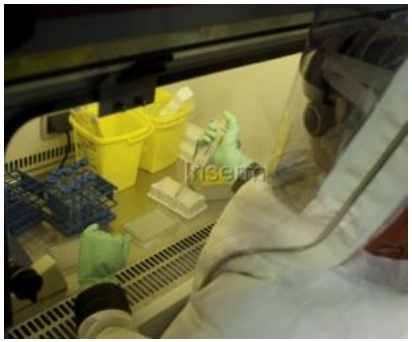
French National Reference Center for Viral Haemorrhagic Fevers

Dr Delphine PANNETIER

Workshop on Emerging Infectious Diseases – Istanbul – 26th march 2026

French NRC for VHF

Directed by Pasteur Institut (UBIVE)
Associated Laboratory : Inserm Jean Mérieux BSL4 Laboratory



Front line in the French healthcare system

Diagnostic Expertise for RG4 viruses (VHF and Nipah)

Advices to health and security authorities

Epidemiological Surveillance

Participation to Alert

Viral Haemorrhagic Fevers

Similar clinical forms observed : fever associated with hemorrhages and multiorgans/cardiovascular failure for the most severe cases

Induced by 3 families of RNA viruses

Flavivirus

Yellow Fever Virus
Dengue Virus
Alkhurma Virus
Omsk Virus
Kyasanur Forest Virus

† <5%

Bunyavirales

Nairovirus
CCHF Virus (Crimean-Congo)

Phenuivirus
Rift Valley Virus

Hantavirus

† 10-50%

Arenavirus
Lassa Virus
Lujo Virus

Junin Virus
Machupo Virus
Guanarito Virus
Sabia Virus

† 10-15%

Filovirus

Ebola Virus
Ebola Zaïre
Ebola Soudan
Ebola Reston
Ebola Bundibugyo
Ebola Taï Forest

Marburg Virus

† 50-90%

No really effective treatment, very limited vaccines

VHF are zoonoses

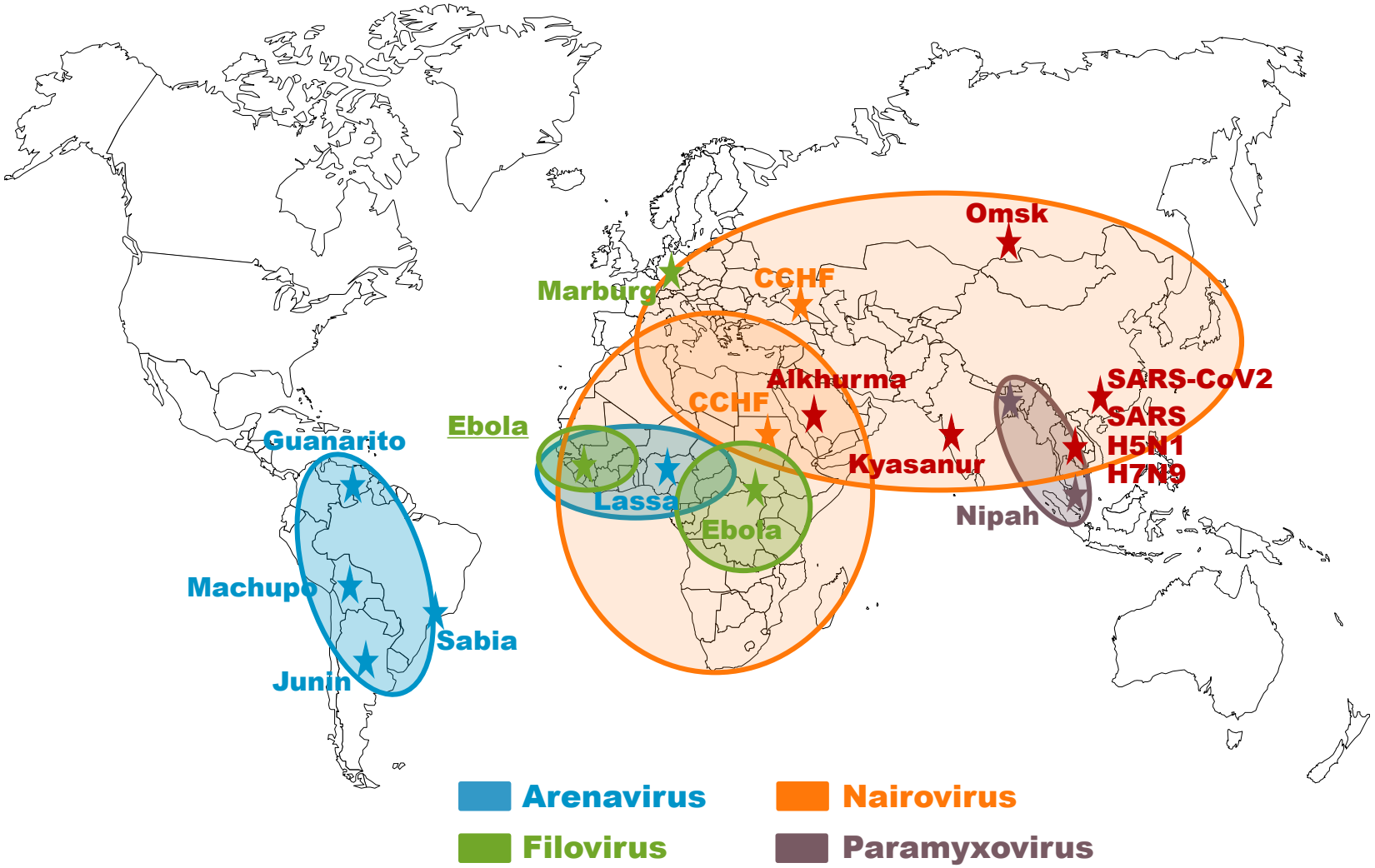
Diseases that normally affect animals with only accidental transmission to humans via animal reservoirs or arthropod vectors

Arboviruses		Other viruses	
Disease	**Vector**	**Disease**	**Reservoir**
Yellow Fever Dengue Rift Valley Fever	Mosquitoes	**Marburg** **Ebola** **(Nipah)**	Bats
CCHF Kyasanur Omsk	Ticks	**Lassa** **New World VHF** FHSR	Rodents

RG4 viruses : human-to-human transmission

➡ **The presence of reservoirs and vectors will influence the geographical distribution of VHF**

Emergence and geography



Outbreaks 2014-2026

VIRUS	YEAR	COUNTRIES
Ebola	2014 2014-2017-2018-2020-2021-2022 2021 2020-2022 2025	Guinea - Sierra Leone - Liberia RDC Guinea Uganda RDC - Uganda
Marburg	2014-2017 2021 2022 2023 2024	Uganda Guinea Ghana Equatorial Guinea – Tanzania Rwanda
Lassa	2016 2017 - 2018 2021 2023 2025 (Lassa-Like)	Benin – Liberia - Nigeria Nigeria - Liberia Guinea Nigeria Chad
CCHF	2014 - 2023 2016 (2013)	Pakistan – Iran – Iraq – Turquie Espagne

Public health problem in constant evolution

Evolution of Emergence

Ebola virus example - 1976

Years	Outbreaks	Confirmed	Deaths
1976 – 2010	19	2291	1525
2011 – 2026	18	32722	13909

Before 2010 : outbreaks each 10 years
Unpredictable West Africa Outbreak 2014-2016
Epidemics are now occurring almost annually…

- Increase of frequency of outbreaks with a larger population at risk of VHF
- Zoonoses : impact related to climate, societal, and environmental changes
- Easier contact between humans and reservoirs (deforestation; changes in animal habits, population movements, etc.)
- Human-to-human transmission
- Risk of imported cases in Europe (travel, expatriates, NGO staff, medical personnel, military personnel, etc.)
- **Expected emergence of CCHF in the coming years in France : confirmation of the presence of CCHF in ticks in the South of France in 2023**

Role of the One Health strategy + surveillance in preventing outbreaks
Early and specific diagnosis is essential to implement rapid isolation measures and prevent the spread of the epidemic.

Symptoms

Incubation
3 to 21 days generally

sudden onset and biphasic evolution

Flu Syndrome
Non-specific Signs

Fever, Chills
Strong Asthenia
Anorexia
Headaches
Arthralgia/Myalgia
Nausea - Vomiting
Diarrhea
Abdominal Pain
Cough

Specific Signs

Skin Rash - Prostration
Gastrointestinal / Respiratory / Vascular Disorders

Internal/External Hemorrhages +++
Epistaxis, petechia, echymoses
DIC – Gingival bleedings
Conjonctivitis - Anuria - Hiccups
Neurological Signs
Multivisceral Disorders
Cardiovascular failure

Death

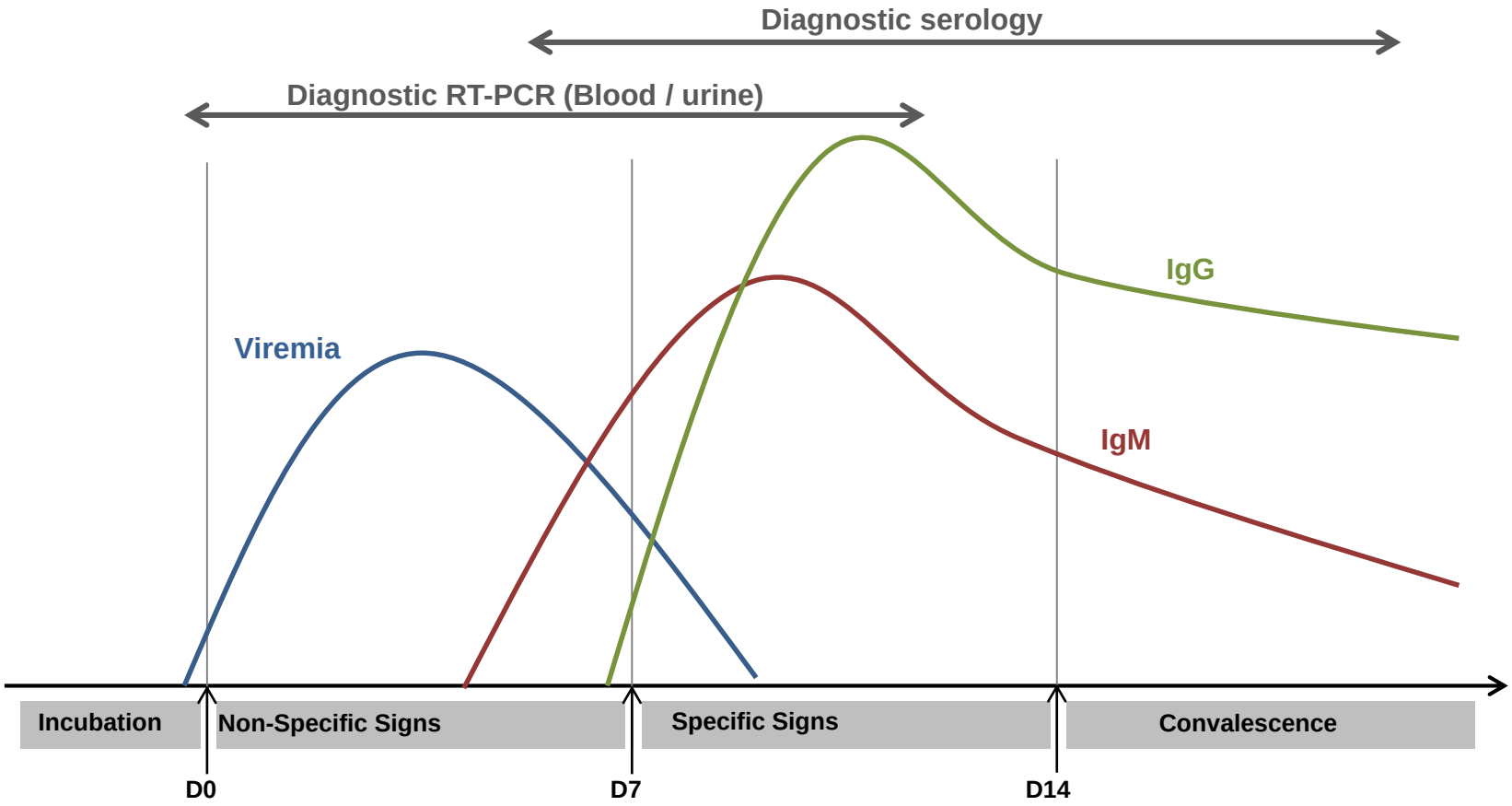
No or light haemorrhagic Signs

Long recovery and lasting effects

Biological Parameters

- **Significant abnormalities of biological parameters**
- **Changes in cell counts**
  - Important lymphopenia/leukopenia
  - Important thrombocytopenia
- **Coagulation disorders**
  - Increased prothrombin time
  - Fibrinolysis disorders
  - Disseminated intravascular coagulation
- **Increase of hepatic enzymes AST / ALT**
- **Proteinuria, hematuria**
- **Increased creatinine and Creatine Kinase levels**
- **Ionic balance disorder**

VHF : viremia and antibodies



Challenges of VHF diagnosis

- **Essential public health mission : primary care unit awereness is fundamental to recognize clinical forms**
  - Always an emergency
  - Need for rapid protective measures for healthcare staff and contact cases
  - Extremely rigorous and costly isolation measures for patient
- **No/few/bad commercial diagnostic tests : in-house technics are essential**
- **Use only reliable and validated techniques : false-negative or false-positive diagnosis impossible because consequences could be dramatic**
- **Perform VHF diagnosis only when necessary to avoid impacting patient care**

In France VHF NRC : initial diagnosis and confirmation

Choice of techniques to implement depends on the area of exposure, clinical signs, and time since the onset of symptoms

Differential Diagnosis
Malaria, Arbovirus, Leptospirosis, Typhoid…

Indirect Tests
Antibodies IgG IgM (ELISA), neutralization, IF

Direct Tests
RT-PCR, viral antigens, virus isolation (BSL4)

Other Tests
Sequencing/NGS, Rapid tests (strips)

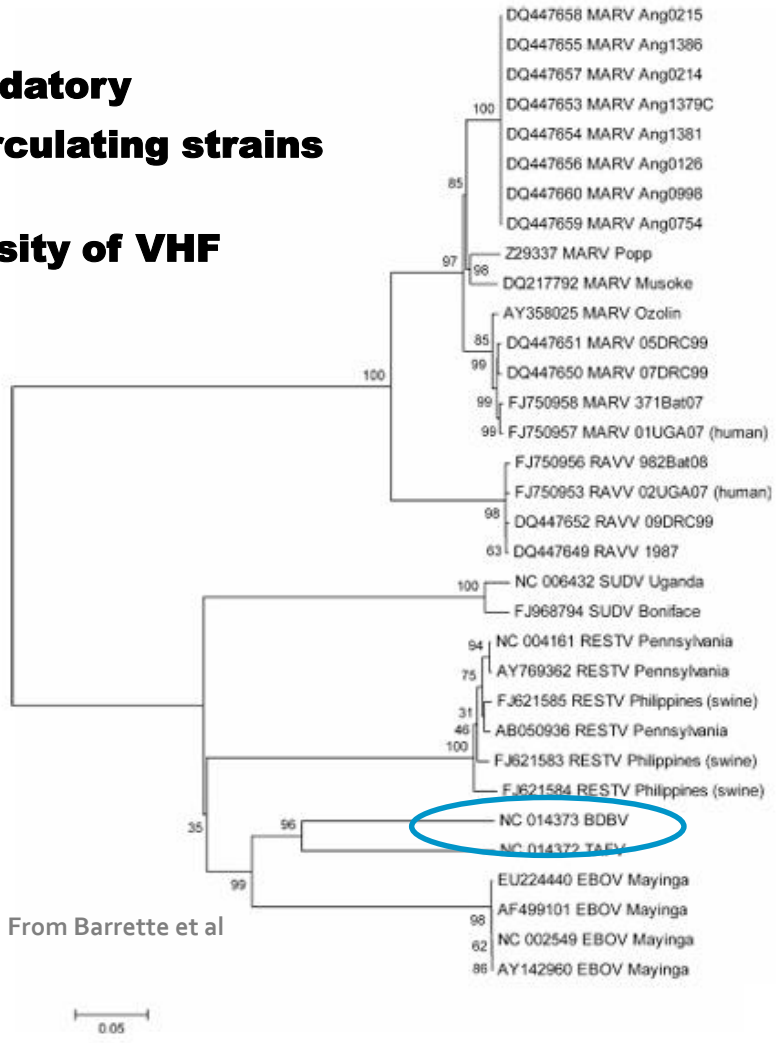
Diagnostic Tests Limitations

Requirements for diagnostic tests

- **Sensitivity and specificity are mandatory**
- **Detection of all strains and last circulating strains essential (human, reservoir, vector)**
- **Difficulties with high genetic diversity of VHF viruses**

→ **Emergence of new strains**

2007 - Bundibugyo Emergence
not detected with the historic filovirus RT-PCR

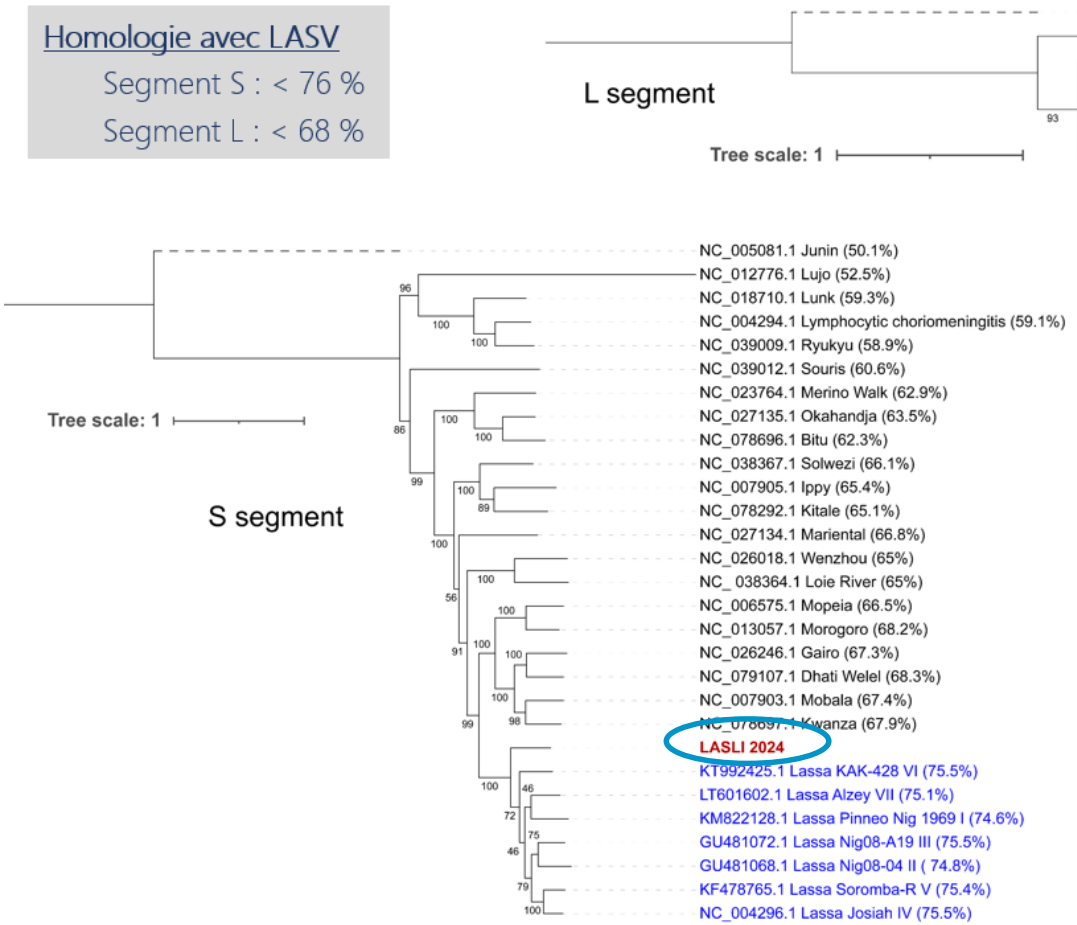


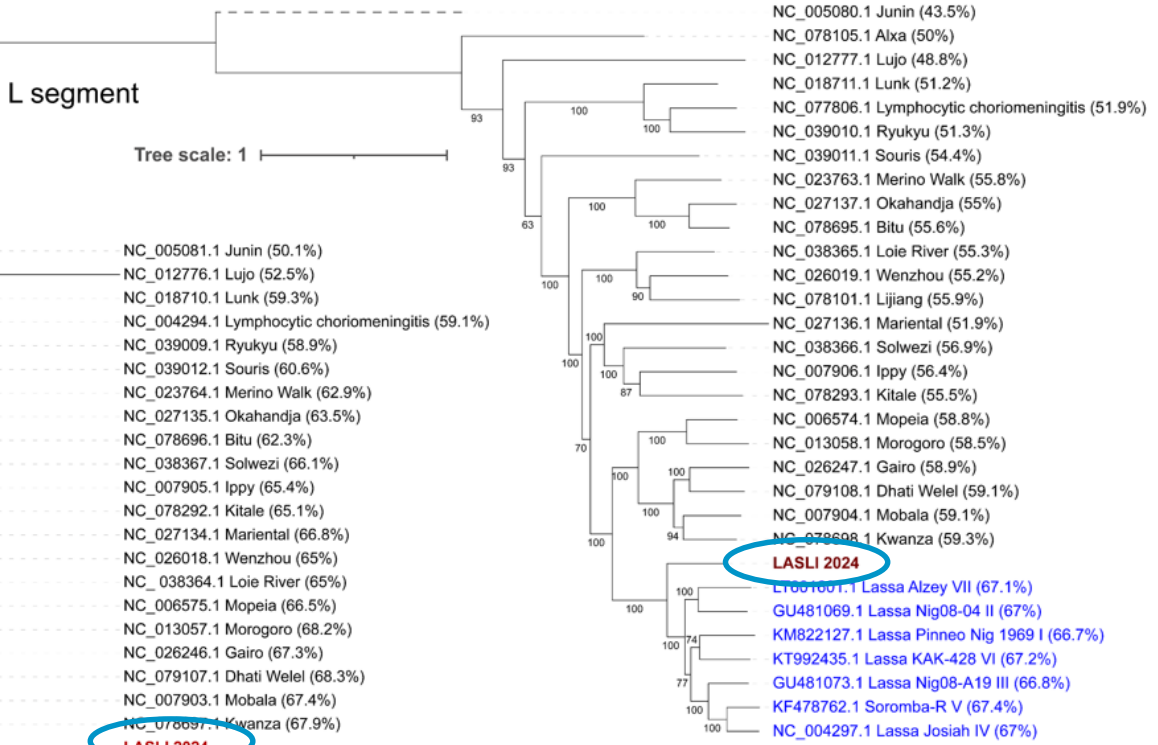
From Barrette et al

Diagnostic Tests Limitations

2025 - Lasli (Lassa-Like Virus) Emergence from Chad : only ½ probes of the Altona kit detect it / No detection with the Biofire Kit

Homologie avec LASV
Segment S : < 76 %
Segment L : < 68 %





The NEW ENGLAND JOURNAL of MEDICINE

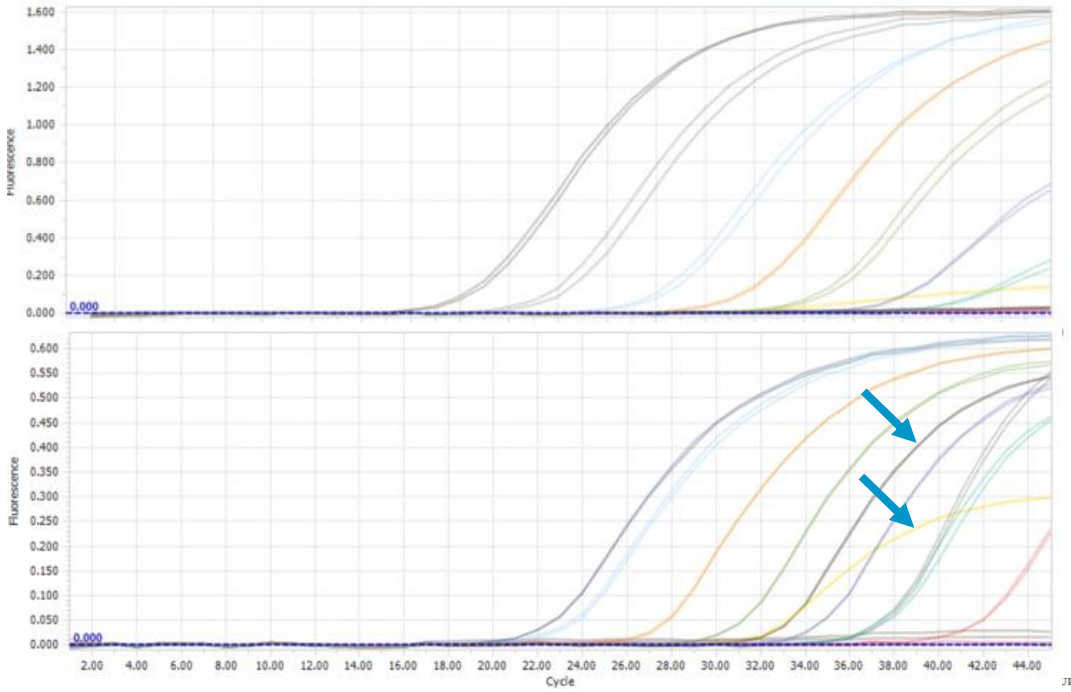
A Mammarenavirus Close to Lassa Virus in a Patient with Meningoencephalitis

Published November 12, 2025 | N Engl J Med 2025;393:1960-1962 | DOI: 10.1056/NEJMc2505127
VOL. 393 NO. 19 | Copyright © 2025

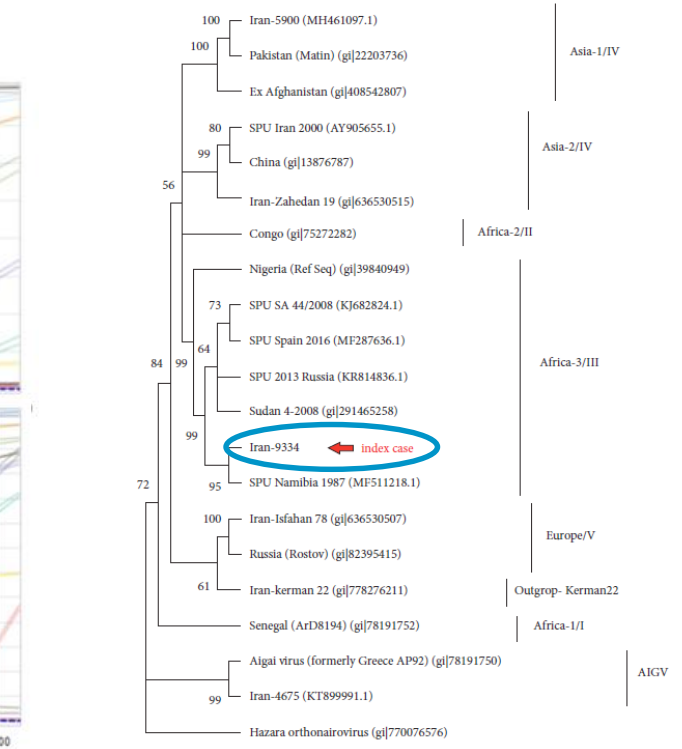
Diagnostic Tests Limitations

Issues With CCHF

- 2021 Spain : Altona kit did not detect the virus in a patient
- 2023 France (Ticks) : RT-PCR from our colleagues does not detect the strain that circulates in ticks
- 2023 Iran : a study from Salehi-Vaziri et al (Pasteur Institut Teheran) reports a clinical case with in-house RT-PCR positive but Real-Star Altona kit negative



France



URE 1: Neighbor-joining phylogenetic tree with bootstrap 5000 and Kimura 2-parameter substitution model indicating that the strain Iran 9334 belongs to CCHFV genotype Africa 3.

Iran

Diagnostic Tests Limitations

Commercial kits : technical data difficult/impossible to obtain

Tested with only few strains NOT REAL STRAINS → not accurate to evaluate sensitivity and specificity in real samples (blood)

BioFire FILMARRAY

Table 10. Limit of Detection for BioFire Global Fever Special Pathogens Panel Test Results

Global Fever Special Pathogens Panel Analyte	Isolate Tested	Live/Inactivated	LoD Concentration	
			Copies/mL[1]	Units/mL
BACTERIA				
Bacillus anthracis	Ames35	Live	4.2E+01	N/A
Francisella tularensis	SCHU S4	Inactivated	1.2E+03	N/A
Leptospira spp.	*interrogans*: serovar icterohaemorrhagiae, Serotype: Budapest	Live	3.4E+02	N/A
Yersinia pestis	A1122	Live	1.3E+02	N/A
VIRUSES				
Chikungunya virus	R86422	Inactivated	5.5E+02	3.6E-01 units/mL
Crimean-Congo hemorrhagic fever virus	Strain IbAr10200	Inactivated	6.4E+00	N/A
Dengue virus	DENV-1: Hawaii	Live	2.2E+02	N/A
	DENV-2-1: New Guinea C	Live	3.4E+02	N/A
	DENV-2-2: Dak AR A1247	Live	2.7E+03	1.5E+02 $TCID_{50}$/mL
	DENV-3: H87	Live	1.3E+02	3.7E+00 units/mL
	DENV-4: H241	Live	6.4E+01	1.8E+02 units/mL
Ebolavirus spp.	Bundibugyo: 200706291 Uganda	Inactivated	7.0E+04	N/A
	Taï Forest: Cote d'Ivoire 11/27/94	Inactivated	8.3E+03	N/A
	Reston: 119810 RIID (MKY 53) (prototype 1989)	Inactivated	2.7E+04	N/A
	Sudan: Boniface	Inactivated	1.1E+04	N/A
	Zaire: Gueckedou/Guinea C07	Inactivated	1.0E+02	1.5E+02 PFU/mL
Lassa virus	Josiah	Inactivated	5.6E+04	N/A
Marburgvirus	Marburg virus: Musoke	Inactivated	5.0E+02	N/A
	Ravn virus: Kenya Ravn	Inactivated	2.6E+02	N/A
West Nile virus	NY 2001-6263 (Lineage 1)	Inactivated	1.1E+03	2.7E+01 units/mL
	B-956 Uganda (Lineage 2)	Inactivated	2.3E+04	6.2E+00 units/mL
Yellow fever virus	Strain 17D	Live attenuated	1.2E+02	1.2E+01 $TCID_{50}$/mL
PROTOZOA				
Leishmania spp.	*donovani*: 9515 (MHOM/IN/95/9515)	Live	1.0E+01	2.2E+01 cells/mL
Plasmodium spp.	*falciparum*, IPC 4884 Pursat Cambodia 2011	Live	1.8E+02	N/A
	knowlesi, H strain	gDNA	2.4E+01	20 pg/mL
	malariae (Clinical Specimen)	Live	1.9E+02	2.3E-01 cells/mL
	ovale, *wallikeri* (Clinical Specimen)	Live	2.4E+02	N/A
	vivax, Strain Chesson	Live	1.5E+02	N/A
Plasmodium falciparum	IPC 4884 Pursat Cambodia 2011	Live	1.8E+02	N/A
Plasmodium vivax/ovale	*ovale*, *wallikeri* (Clinical Specimen)	Live	2.4E+02	N/A
	vivax, Strain Chesson	Live	1.5E+02	N/A

[1] Stock concentrations determined using commercially available quantitative real-time PCR assay kits.

Conclusions

- **Be ready as soon as possible, before human emergence if possible : importance of the One Health Strategy**

- **No/few commercial kits or not really validated :**
  BE REALLY CAREFUL USING IT

- **Diversity of VHF viruses with regular emergence of new species and new variants → updating and validation of techniques necessary**

- **Need for epidemiological surveillance and detailed, up-to-date epidemiological knowledge about GR4 agents → sharing informations about diagnosis, epidemiology and kits is very important**

- **Accreditation of laboratory tests can be difficult due to a lack of samples when you are not in endemic area**

- **French MOT regulation concerning VHF viruses to be taken into account (time-consuming administrative burden / influence on management of confirmed cases)**

- **New European IVD regulation on in vitro diagnostic tests : probleme for in house tests to prove they are better than commercial kits**

Thank you