Collaboration to Drive Optimized Supportive Care for Lassa Fever

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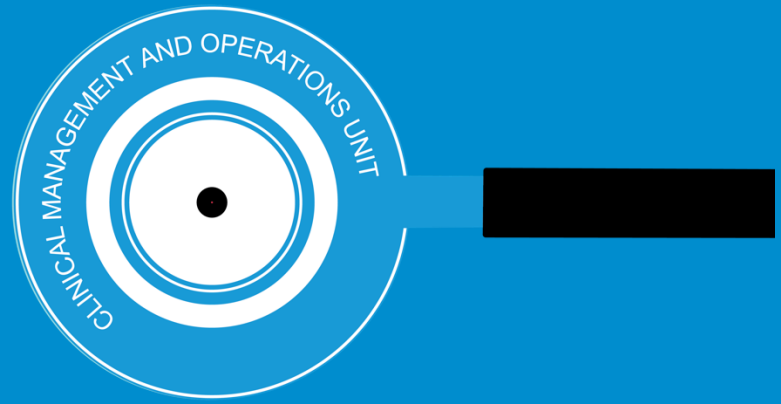

World Health Organization

HEALTH EMERGENCIES programme

Benefits of a Research Collaboration on Clinical Care for Lassa Fever

Better understanding of the mechanisms driving clinical complications can improve supportive care

Identification of populations at risk can improve prevention of clinical complications

Allows for the establishment of standards of care for LF

Improved efficiency of clinical response

What do we know?

Lassa fever outcomes and prognostic factors in Nigeria (LASCOPE): a prospective cohort study

Alexandre Duvignaud, Marie Jaspard*, Ijeoma Chukwudumebi Etafo, Delphine Gabillard, Béatrice Serra, Chukwuyem Abejegah, Camille le Gal, Abiodun Tolani Abidoye, Mahamadou Doutchi, Sampson Owhin, Benjamin Séri, Jackson Katembo Vihundira, Marion Bérerd-Camara, Justine Schaeffer, Nicolas Danet, Augustin Augier, Ephraim Ogbaini-Emovon, Alex Paddy Salam, Liasu Adeagbo Ahmed, Sophie Duraffour, Peter Horby, Stephan Günther, Akinola Nelson Adedosu, Oladele Oluwafemi Ayodeji†, Xavier Anglaret†, Denis Malvy†, on behalf of the LASCOPE study group‡*

Clinical and laboratory predictors of Lassa fever outcome in a dedicated treatment facility in Nigeria: a retrospective, observational cohort study

Peter Okokhere, Andres Colubri, Chukwuemeka Azubike, Christopher Iruolagbe, Omoregie Osazuwa, Shervin Tabrizi, Elizabeth Chin, Sara Asad, Ehi Ediale, Mojeed Rafiu, Donatus Adomeh, Ikponmwosa Odia, Rebecca Atafo, Chris Aire, Sylvanus Okogbenin, Meike Pahlman, Beate Becker-Ziaja, Danny Asogun, Terrence Fradet, Ben Fry, Stephen F Schaffner, Christian Happi, George Akpede, Stephan Günther, Pardis C Sabeti

Factors associated with progression to death in patients with Lassa fever in Nigeria: an observational study

Jamie Strampe, Danny A Asogun, Emily Speranza, Meike Pahlmann, Ali Soucy, Sabrina Bockholt, Elisa Pallasch, Beate Becker-Ziaja, Sophie Duraffour, Nahid Bhadelia, Yemisi Ighodalo, Jennifer Oyakhilome, Emmanuel O Omomoh, Thomas Olokor, Donatus I Adomeh, Odia Ikponwonsa, Chris Aire, Ekaete Tobin, Nosa Akpede, Peter O Okokhere, Sylvanus A Okogbenin, George O Akpede, César Muñoz-Fontela Ephraim Ogbaini-Emovon, Stephan Günther, John H Connor, Lisa Oestereich

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Delirium/coma/seizure	2-16%
Dizziness	25-29%

Oxygen saturation <92%	7-15%
Oxygen supplementation	18%
Duration	3d (2-7)

Systolic BP <90mmHg	5-22%

Glucose <54mg/dl	7-15%
AST>3xUL	38-41%

No dysfunction	83-87%
ARF	2-28%
RRT	8%

Bleeding	19-34%
Platelets <80	11-14%

Host and Disease-Related Factors Associated with Mortality

- Age
- Organ injury
  - ARF
  - Liver injury
  - Bleeding
  - Severe CNS disease?
- Viral Load

	Available data in the univariable analysis	Participants who died	Univariable		Multivariable	
			Crude odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p value
Sex						
Female	252	28 (11%)	1 (ref)	..	1 (ref)	..
Male	258	34 (13%)	1·21 (0·71–2·07)	0·48	1·19(0·45–3·16)	0·72
Age, years						
<45	361	25 (7%)	1 (ref)	..	1 (ref)	..
≥45	149	37 (25%)	4·44 (2·56–7·70)	<0·0001	16·30 (5·31–50·30)	<0·0001
NEWS2						
<7	419	30 (7%)	1 (ref)	..	1 (ref)	..
≥7	65	30 (46%)	11·10 (6·02–20·50)	<0·0001	4·79 (1·75–13·10)	0·0023
Plasma ALT						
<3 ULN	341	21 (6%)	1 (ref)	..	1 (ref)	..
≥3 ULN	80	23 (29%)	6·15 (3·19–11·80)	<0·0001	4·96 (1·69–14·60)	0·0036
KDIGO stage						
<2	442	26 (6%)	1 (ref)	..	1 (ref)	..
≥2	53	28 (53%)	17·90 (9·18–35·00)	<0·0001	7·52 (2·66–21·20)	<0·0001
Lassa RT-PCR Ct						
≥30	290	8 (3%)	1 (ref)	..	1 (ref)	..
<30	176	46 (26%)	12·50 (5·72–27·20)	<0·0001	4·65 (1·50–14·50)	0·0078

World Health Organization

Duvignaud, A Lancet ID 2022
Okokhere Lancet ID 2018
Strampe Lancet ID 2021

Optimized Supportive Care

- 18% received oxygen
  - ~6L for 2-7 days
- Vasopressors?
- 8% received RRT
  - Azotemia for 2 sessions
  - CFR 56%
- 31% received blood transfusions
  - ~2 pints
- 90% received antibiotics

Oxygen‡	
Received	92 (18%)
Maximum output, L/min	6 (5–6)
Duration, days	3 (2–7)
Total blood transfusion§	
Received	158 (31%)
Number of units (total blood pints)	2 (2–4)
Renal replacement therapy (intermittent haemodialysis)	
Received	42 (8%)
Indications¶	
Fluid overload, no response to diuretics	5 (14%)
Symptomatic hyperazotaemia	33 (94%)
Severe acid-base disorder not responding to medical treatment	1 (3%)
Number of sessions	2 (1–4)
Outcome	
Died	23 (56%)
Survived	18 (44%)
Antibacterial therapy	
Received	459 (90%)
Duration, days	8 (7–10)
Antimalarial therapy‖	
Received	188 (37%)

Duvignaud, A Lancet ID 2022

LASV Dissemination and Pathology

Table 1—Organ Viral Titers* and Selected Clinical Laboratory Data

Case	Blood	Liver	Spleen	Lung	Kidney	Adrenal	Others	AST†	ALT‡	CPK§	BUN‖	Amylase¶
1	6.5	0	–	–	–	–	–	1124	131	1604	15	270
2	≥5.0	0	0	–	3.5	–	PI-6.5	2688	305	208	67	30
3	6.1	–	–	–	–	–	–	–	–	–	–	–
4	≥2.9	–	–	–	–	–		965	–	–	–	–
5	5.6	2.5	–	–	4.6	–	BM-4.6	3966	1455	4568	76	–
6	5.5	6.0	5.5	6.5	6.0	4.0	MG-7.0, 0-6.0, H-5.5, LN-4.5, Pa-4.0, SG-3.5	–	–	–	–	–
9	5.1	0	–	–	–	–	–	2336	299	297	66	1120
10	7.0	6.5	3.5	–	6.5	–	–	–	441	–	–	–
11	6.6	–	–	–	–	–	–	1641	183	611	41	68
12	5.6	–	–	–	–	–	PI-4.6	8	258	305	54	–
13	–	–	–	–	–	–	–	56	37	45	8	38
14	6.1	9.0	9.0	9.0	7.0	–	H-6.5, B-4.5, Pa-4.5	–	–	–	–	–
15	8.1	8.5	7.0	6.5	6.5	6.5	PI-8.0, Pa-6.5, H-6.0, B-5.5	–	–	–	–	–
16	0	0	–	–	4.5	–	–	–	–	–	–	–
17	4.6	–	–	–	–	–	–	687	94	>10,000	74	1325
20	5.1	6.5	–	–	–	–	–	–	–	–	–	–
Fetus 1	–	0	2.0	–	4.0	–	T-0	–	–	–	–	–
Fetus 2	–	0	0	–	0	–	H,Pa,T,PI-0	–	–	–	–	–
Fetus 3	3.5	–	4.8	3.8	3.0	–	PI-7.5	–	–	–	–	–

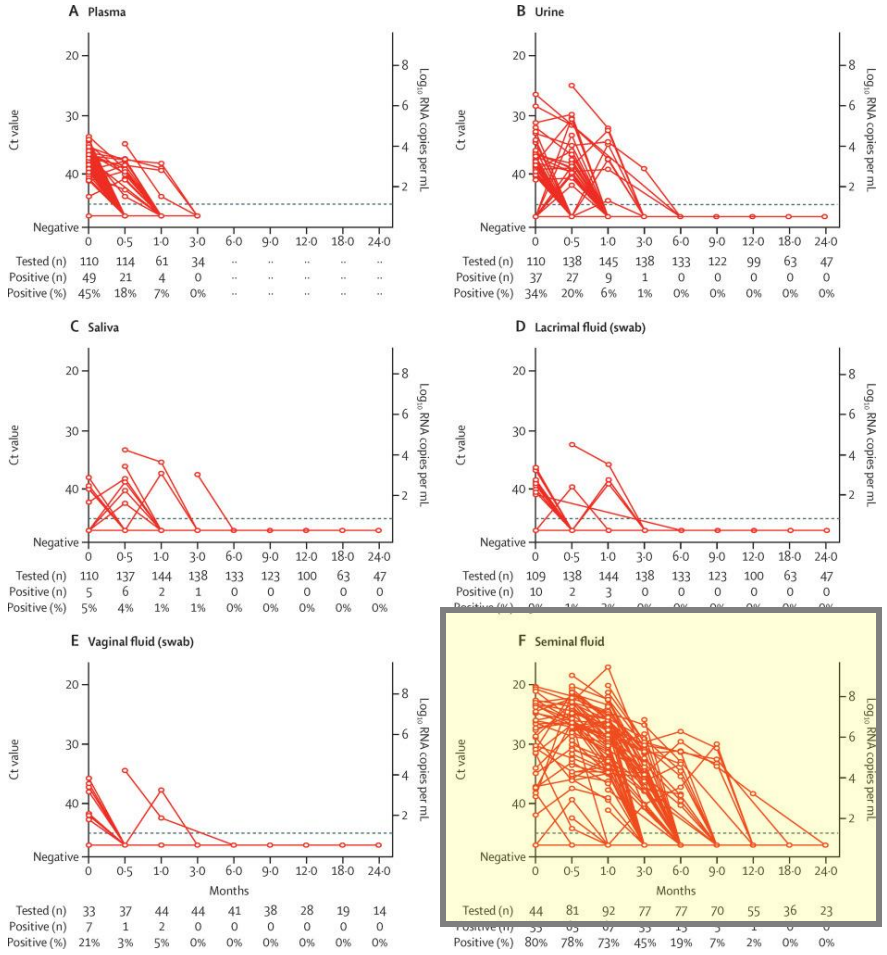
Table 3—A Comparison of Extrahepatic Lesions Reported in Human Arenaviral Infections

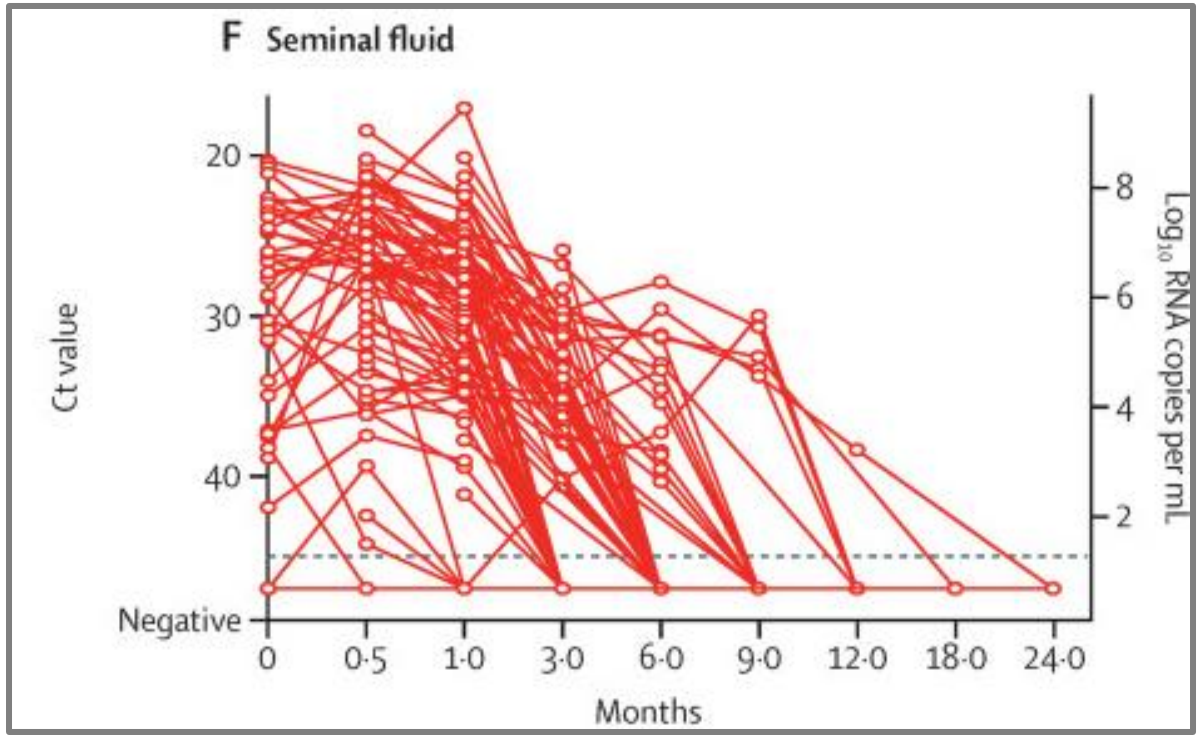
Lesion	Lassa fever*	AHF	BHF	LCM
Splenic necrosis	11/12 (8/8)	0/12	0/8	–
Renal lesions	7/13 (6/9)	6/12	2/8	–
Adrenal necrosis	3/6 (3/3)	0/12	–	–
Adrenal inclusions	3/6 (3/3)	0/12	–	–
Myocarditis	3/9 (3/5)	4/12	–	0/1
Interstitial pneumonia	4/10 (2/6)	4/12	6/6	3/3
Myositis	5/15 (5/15)	–	–	–
Encephalitis	0/4 (0/3)	5/12	6/6	2/3

** Brain, Heart, Kidney, Bone Marrow, Placenta, Mammary gland

Walker, D. AJP 1989

LASV Compartmentalization + Persistence





35 (80%) of 44 M had LASV RNA in seminal fluid at month 0 with a median cycle threshold of 26·5. Lassa virus RNA remained detectable **up to month 12** in seminal fluid

Thielebein, A Lancet Microbe 2022

Acute Kidney Injury Review

What are the key clinical questions we need to answer to improve LF care?

Delirium/coma/seizure **2-16%**
Dizziness **25-29%**

1. Direct viral injury
2. Hypoglycemia
3. Elyte abnormalities
4. Medications

Oxygen saturation <92% **7-15%**
Oxygen supplementation **18%**
Duration **3d (2-7)**

1. Fluid resuscitation?
2. Acidosis

Systolic BP <90mmHg **5-22%**

1. Fluid responsive?
2. Myocardial dysfunction
3. Myocarditis?

Glucose <54mg/dl **7-15%**
AST>3xUL **38-41%**

1. Hepatic dysfunction?
2. Glycogen depletion?

No dysfunction **83-87%**
ARF **2-28%**
RRT **8%**

1. Late presentation
2. Fluid resuscitation?
3. Acidosis

Bleeding **19-34%**
Platelets <80 **11-14%**

1. DIC?
2. Platelet dysfunction

Long-term Sequelae + Subgroups

- Sensorineural hearing loss
- Other post-LF complications
- Viral persistence

- Pregnant people
- <5 years of age
- >50 years of age

- Virus Lineage and outcomes

What research studies are actively addressing these gaps to improve clinical care?

Is there interest in a collaboration

+

Important research gaps related to LF clinical care?

Clinical Research Collaboration in Public Health Emergencies

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Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

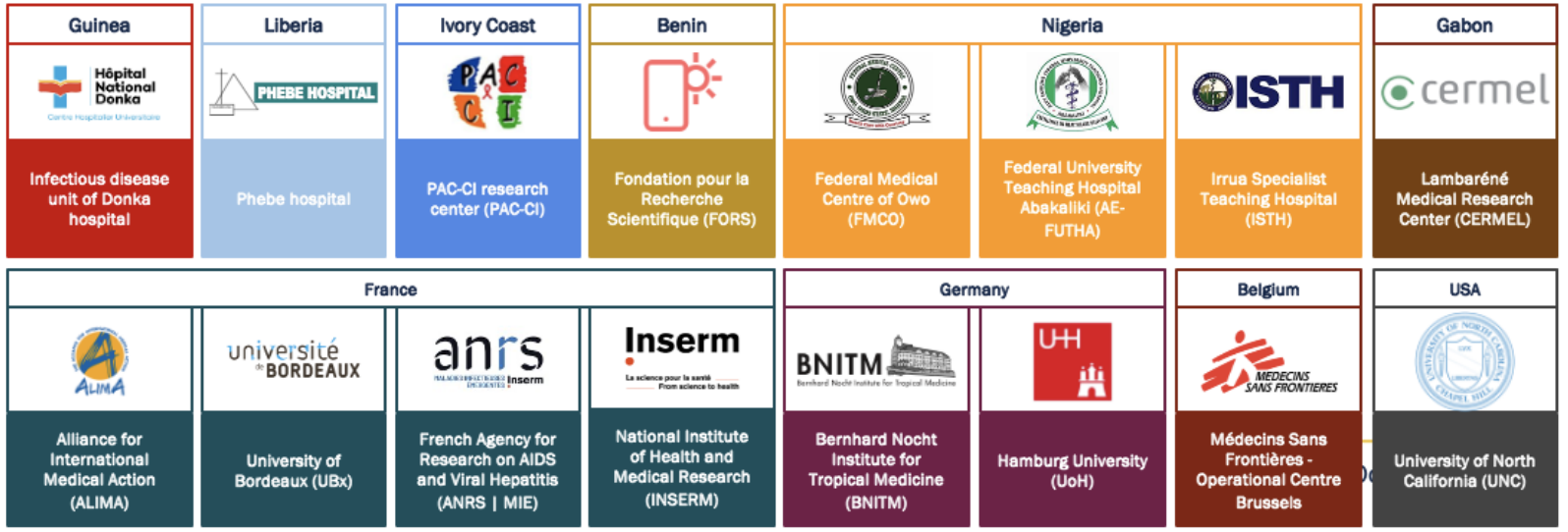
The REMAP-CAP, ACTIV-4a, and ATTACC Investigators*

Correspondence

https://doi.org/10.1038/s41591-023-02393-6

The international Unity study for antivirals against mpox is a blueprint for future epidemics

INTEGRATE



Action Plan – One Approach

Goal: Establish a clinical research collaboration to define the mechanisms underlying organ failure + characterize natural history in high-risk subgroups to inform better supportive care

Develop subspeciality working groups to characterize LF-specific complications and define mechanisms of disease

- Neuro → glucose, electrolytes, lumbar puncture
- Cardiovascular → ECHO + IVC, troponin, EKG
- Renal → FeUrea, urine microscopy, UA, CK
- Coagulopathy → Fibrinogen, INR, PTT, ROTEM
- Pregnancy
- <5 years of age
- >50 years of age
- *Virus Lineages and outcomes

Next Steps

- Identify working group leads and working groups
- Generate key data fields to answer clinical questions
- Funding
- Meeting cadence