[Nearly] 50 years of Lassa fever: The road ahead

Robert F. Garry, PhD
Tulane University
Zalgen Labs
February 1969 - deadly unidentified virus reported from remote African missionary hospital, two American nurses stricken and died within 10 days. Doctors stymied by mysterious symptoms of the killer: soaring temperature, painful backache, swelling of the throat and neck, discolored skin! Latest victim airlifted to special isolation ward at New York's Columbia Presbyterian Hospital, blood samples rushed to Yale's Arborvirus [sic] Laboratory, all-out search launches to discover an antidote. U. S. Public Health officials alarmed, virus has the potential to decimate the whole population, aviation officials consider cancellation of all jet travel to critical world areas.
LASSA FEVER, A NEW VIRUS DISEASE OF MAN FROM WEST AFRICA

II. REPORT OF A LABORATORY-ACQUIRED INFECTION TREATED WITH PLASMA FROM A PERSON RECENTLY RECOVERED FROM THE DISEASE

EDGAR LEIFER, DAVID J. GOCKE, AND HENRY BOURNE
Department of Medicine, Columbia University College of Physicians and Surgeons, and The Presbyterian Hospital, New York, New York 10032

LASSA FEVER, A NEW VIRUS DISEASE OF MAN FROM WEST AFRICA

III. ISOLATION AND CHARACTERIZATION OF THE VIRUS*

SONJA M. BUCKLEY AND JORDI CASALS
Yale Arbovirus Research Unit, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut 06510, and The Rockefeller Foundation, New York, N.Y. 10020
## Table 1
Source of materials, and isolations of Lassa virus

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Locale of infection</th>
<th>Date of onset, 1969</th>
<th>Outcome of infection</th>
<th>Material, and date collected</th>
<th>Isolation in Vero cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.W.</td>
<td>F</td>
<td>Lassa, Nigeria</td>
<td>20 Jan.</td>
<td>Death, day 6</td>
<td>Serum, 26 Jan.</td>
<td>(day 6) +</td>
</tr>
<tr>
<td>C.S.</td>
<td>F</td>
<td>Jos, Nigeria</td>
<td>3 Feb.</td>
<td>Death, day 10</td>
<td>Serum, 6 Feb.</td>
<td>(day 3) +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Serum, 13 Feb.</td>
<td>(day 10) +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Serum, 5 March</td>
<td>(day 13) +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pleural fluid, 5 March</td>
<td>(day 13) +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Serum, 6 March</td>
<td>(day 14) +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Serum, 20 March</td>
<td>(day 28) 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Serum, 29 March</td>
<td>(day 37) 0</td>
</tr>
<tr>
<td>J.C.</td>
<td>M</td>
<td>New Haven, Conn.</td>
<td>9 June</td>
<td>Recovery*</td>
<td>Serum, 16 June</td>
<td>(day 7) +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Serum, 18 June</td>
<td>(day 9) +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Urine, 18 June</td>
<td>(day 9) +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Throat washing, 18 June</td>
<td>(day 9) +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Throat washing, 23 June</td>
<td>(day 14) +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Urine, 26 June</td>
<td>(day 17) +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Urine, 11 July</td>
<td>(day 32) +</td>
</tr>
<tr>
<td>N.Y.</td>
<td>F</td>
<td>—</td>
<td>—</td>
<td>Recovery*</td>
<td>Serum, 26 Feb. '69</td>
<td>0</td>
</tr>
<tr>
<td>C.C.</td>
<td>F</td>
<td>—</td>
<td>—</td>
<td>Stationed in Nigeria</td>
<td>Serum, 23 Sept. '68</td>
<td>0</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diluent</td>
<td>0</td>
</tr>
</tbody>
</table>
Penny with Jordi Casals and Raphael Adeyemi, a Nigerian Medical auxiliary, at the hospital in Jos, Nigeria, circa 1970.
NOTES

Arenoviruses: Proposed Name for a Newly Defined Virus Group

WALLACE P. ROWE, FREDERICK A. MURPHY, GERNOT H. BERGOLD, JORDI CASALS, JOHN HOTCHIN, KARL M. JOHNSON, FRITZ LEHMANN-GRUBE, CEDRIC A. MIMS, ERIC TRAUB, AND PATRICIA A. WEBB

National Institute of Allergy and Infectious Diseases, Bethesda, Maryland; National Communicable Disease Center, Atlanta, Georgia; Instituto Venezolano de Investigaciones Científicas, Caracas, Venezuela; Yale University School of Medicine, New Haven, Connecticut; New York State Department of Health, Albany, New York; Middle America Research Unit, Balboa Heights, Canal Zone; Hygiene-Institut der Philipps-Universität, Marburg/Lahn, Germany; John Curtin School of Medical Research, Canberra, Australia; and United Nations Food and Agricultural Organization, Ankara, Turkey

Received for publication 23 March 1970

The name “arenoviruses” is proposed for the newly defined taxonomic group containing lymphocytic choriomeningitis, Lassa, and the Tacaribe complex viruses.
70% case fatality rate in patients presenting while viremic (Shaffer et al., 2014).
Lassa fever is a zoonosis

*Mastomys natalensis* (multimammate “rat”)

Lassa fever is acquired through contact with excreta or the preparation of “rat” for food

Photo credits: Lina Moses, PhD Tulane
Where we work in West Africa

Sites in Sierra Leone and Nigeria

Christian Happi
First EVD Nigeria
July 20, 2014

Augustine Goba
First EVD Sierra Leone
May 25, 2014

Kristian Andersen et al. 2015
Lassa fever program at Kenema Government Hospital

- Important site for Lassa fever research by CDC and others
- Blood Diamonds civil conflict forces suspension of Lassa program
- International team refurbishes Lassa Laboratory
- Establishment of recombinant Lassa ELISA diagnostics
- Introduction of ReLASV lateral flow immunoassays

Timeline:
- 1970s and 1980s
- 1993
- 2005
- 2008
- 2010
Lassa fever diagnosis

LASV antigen, LASV RNA or antiLASV antibody

Ebola came to us [over ten years ago]
Kenema: Early epicenter of the 2013-16 Ebola Outbreak

Kenema Government Hospital

Dr. S. Humarr Khan
Healer

Nurse Will Pooley

Dr. Ian Crozier
Roots, Not Parachutes: Research Collaborations Combat Outbreaks

Nathan L. Yozwiak, Christian T. Happi, Donald S. Grant, John S. Schieffelin, Robert F. Garry, Pardis C. Sabeti, Kristian G. Andersen

Cell
Volume 166, Issue 1, Pages 5-8 (June 2016)
DOI: 10.1016/j.cell.2016.06.029
Dr. S. Humarr Khan

Dr. Christian Happi

Dr. Pardis Sabeti

Bob

May 14, 2014

ACEGID
African Center of Excellence for Genomics of Infectious Diseases
Redeemer’s University, Nigeria
“Confirmed” cases of Lassa fever in Nigeria

Siddle et al. NEJM, Oct. 17, 2018
21 (of 36) states have recorded at least one confirmed case of Ebola.

Africans sequencing on African soil in real-time.

1 dot = confirmed case

1-50 confirmed cases
>50 confirmed cases
No confirmed cases
It’s all about the rodent transmission.
KGH Viral Hemorrhagic Fever Ecology Team
JUST BACK FROM NIGERIA
Most neutralizing human monoclonal antibodies target novel epitopes requiring both Lassa virus glycoprotein subunits

The best antibodies bind this (Erica)

Lassa virus B cell epitopes and how the work

Binding blocks dystroglycan interaction

Binding is non-neutralizing

Binding blocks fusion

Kathryn M. Hastie, Erica Ollmann Saphire and Michelle A. Zandonatti

Erica and Kate
3 huMabs down-selected to 2
• Bispecific huMAbs work
• Effective at 1.5 mg/Kg against diverse lineages
• Rationally engineered Mabs in pipeline (Erica/Kate)
Khan Center of Excellence (NIH- ICIDR)

Dr. Donald S. Grant

Simbirie Jalloh
Bilateral Hearing loss in both Ebola and Lassa fever survivors

<table>
<thead>
<tr>
<th>Hearing Loss Severity</th>
<th>Ebola Survivors (%)</th>
<th>Ebola Contacts (%)</th>
<th>Lassa Survivors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 342</td>
<td>n = 850</td>
<td>n = 57</td>
</tr>
<tr>
<td>Normal</td>
<td>222 (64.9)</td>
<td>685 (80.6)</td>
<td>35 (61.4)</td>
</tr>
<tr>
<td>Mild</td>
<td>105 (30.7)</td>
<td>149 (17.5)</td>
<td>5 (8.8)</td>
</tr>
<tr>
<td>Moderate</td>
<td>11 (3.2)</td>
<td>14 (1.7)</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>Severe</td>
<td>3 (0.9)</td>
<td>2 (0.2)</td>
<td>2 (3.5)</td>
</tr>
<tr>
<td>Profound</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
<td>12 (21.1)</td>
</tr>
</tbody>
</table>

** <.001
Polymorphic variants within populations sampled in the 1000 Genomes Project

Ongoing GWAS and other Systems Biology studies in Ebola and Lassa fever (Sabeti/Andersen)

Nature 526, 68–74 (01 October 2015)
Thanks to Georges Thiry for pointing out that Lassa fever is one of 3 epidemic infectious diseases (with Nipah and MERS) prioritized for rapid vaccine development by the Coalition for Epidemic Preparedness and Innovations (CEPI). Indeed, Lassa efficacy trials are possible!
Ongoing antiLASV seroprevalence study in Sierra Leone

- **28 endemic communities** KENEMA
- **20 emerging communities** TONKOLILI
- **20 non-endemic communities** PORT LOKO

1. Enumerate all households in community
2. Randomize households
3. 20+ households
4. 20+ households
5. 20+ households
6. 1 each in 5 age groups
7. 1 each in 5 age groups
8. 1 each in 5 age groups

- Collection of blood spots for IgG testing
- Demographic questionnaire
- Screening of blood spots by ELISA
- Statistical analysis and reporting
High Lassa seroprevalence villages are found across Sierra Leone

House level demographics and serology
LASV sero-prevalence by age

<1  1-4  5-14  15-44  >45

Incidence studies

Active case finding with RDTs
Kenema District: Gateway to the Gola Rainforest.
Single-vector, single injection, bivalent and trivalent rVSV vaccine candidates expressing stabilized LASV GPC and EBOV GP
In memoriam…

In Loving Memory of Dr. SHEIKH H. KHAN
Died: 29th July 2014.
Former. Tulane-Lassa fever VHF-Doctor
Kenema Government Hospital RIP

Photo credit: Pardis Sabeti

Photo credit: Kristian Andersen

Mbalu Fonnie

Alice Kovoma

Mohamed Fullah

Dr S. Humarr Khan