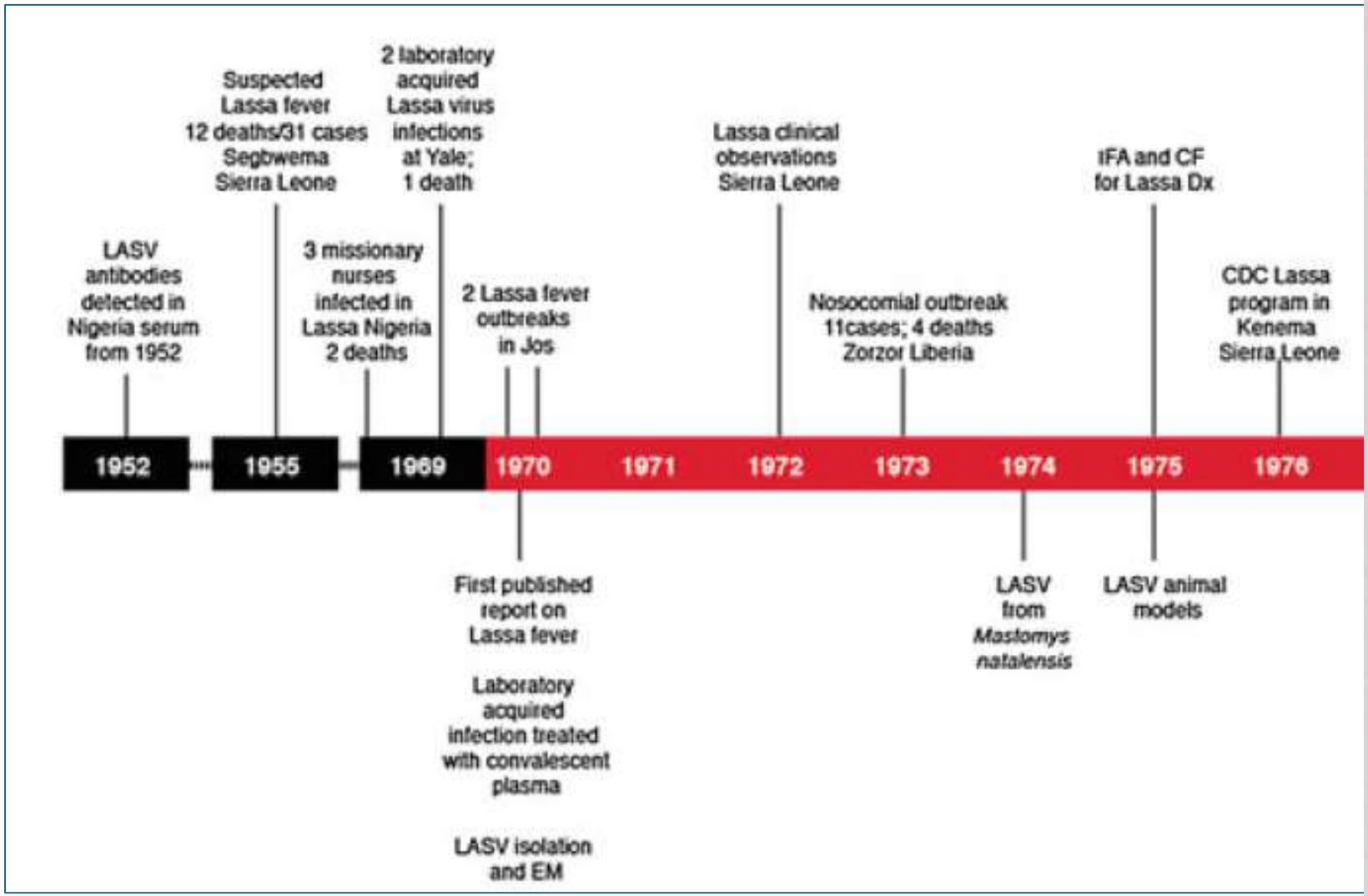
Lassa Ateşi: Güncel Durum

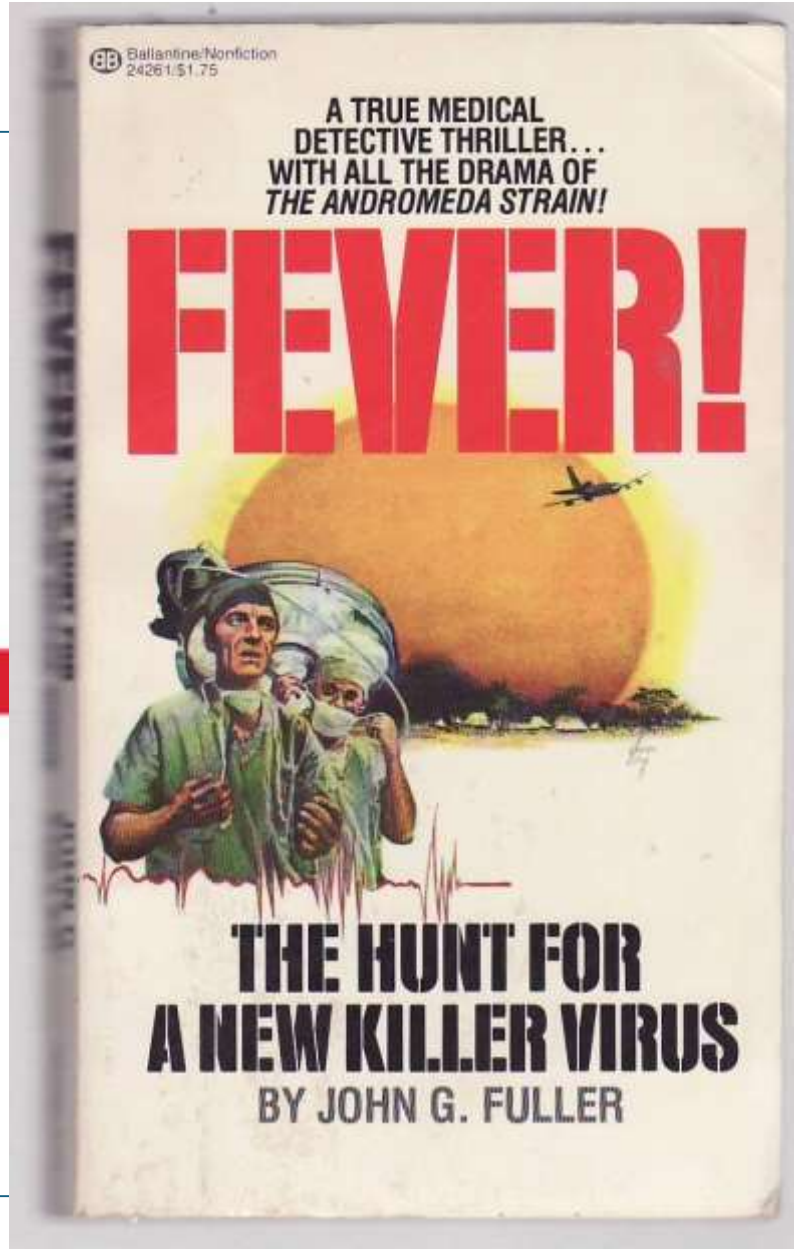
Dr. Şiran Keske

Koç Üniversitesi Tıp Fakültesi

Amerikan Hastanesi

Koç Üniversitesi İş Bankası Enfeksiyon Hastalıkları Merkezi (KUISCID)

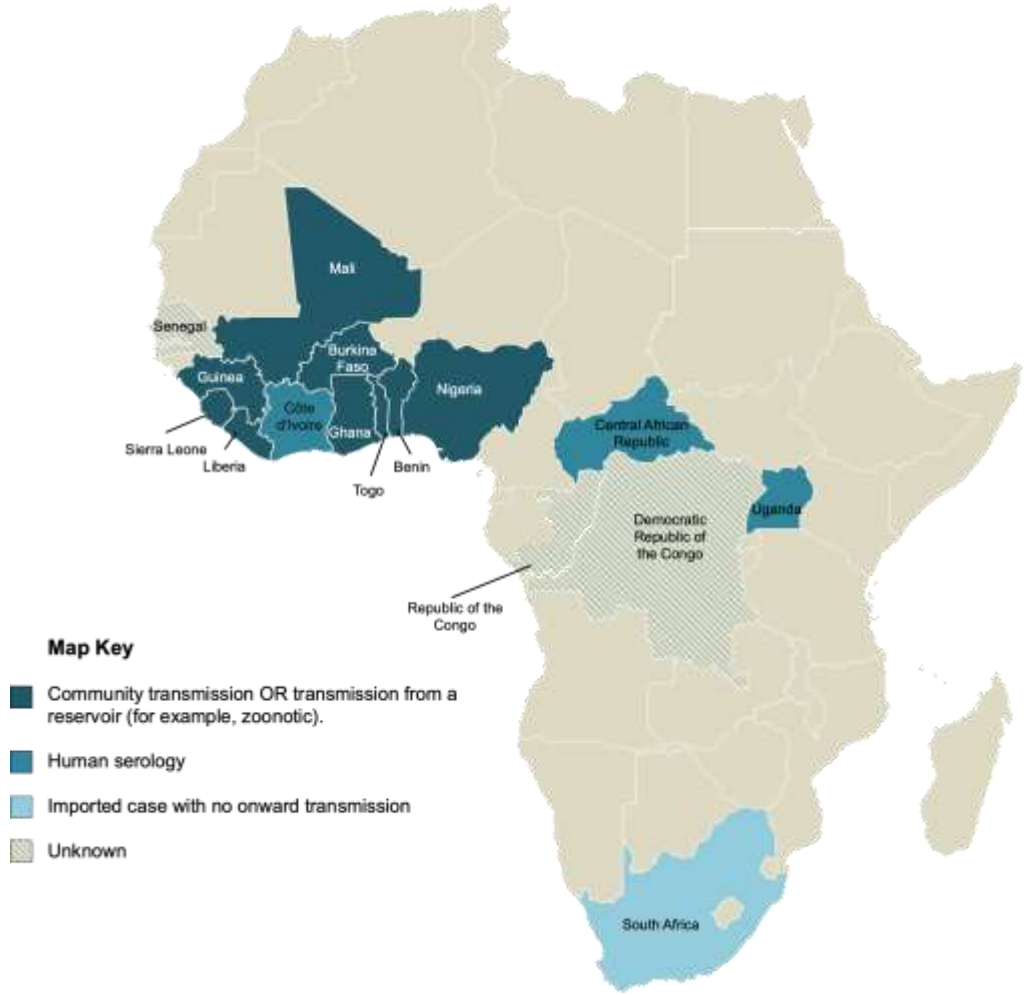




Robert Garry. Lassa fev

Epidemiyoloji

- Nijerya
- Liberya
- Sierra Leone
- Gine
- Gana
- Mali
- Benin
- Togo



https://www.gov.uk/guidance/lassa-fever-origins-reservoirs-transmission-and-guidelines

SARS	Frequency	% $N = 3379$	Crimean-Congo	Frequency	% $N = 766$	Marburg	Frequency	% $N = 354$
China	811	24.0	Turkey	288	37.6	USA	154	43.5
USA	786	23.3	Iran	91	11.9	Germany	65	18.4
Hong Kong	499	14.8	USA	91	11.9	Canada	29	8.2
Taiwan	276	8.2	UK	45	5.9	Japan	23	6.5
Canada	240	7.1	Germany	41	5.4	France	20	5.6
Singapore	211	6.2	Greece	41	5.4	UK	18	5.1
Germany	167	4.9	France	36	4.7	Belgium	13	3.7
UK	131	3.9	Sweden	35	4.6	Switzerland	13	3.7
Japan	127	3.8	Russian Fed.	27	3.5	South Africa	12	3.4
Netherlands	79	2.3	Bulgaria	24	3.1	Congo	11	3.1
Ebola	Frequency	% $N = 2355$	Rift valley fever	Frequency	% $N = 678$	MERS	Frequency	% $N = 613$
USA	1147	48.7	USA	263	38.8	USA	201	32.8
Canada	192	8.2	France	124	18.3	Saudi Arabia	96	15.7
France	192	8.2	South Africa	75	11.1	China	82	13.4
Germany	186	7.9	Kenya	68	10.0	UK	55	9.0
UK	160	6.8	Senegal	46	6.8	Germany	54	8.8
China	122	5.2	UK	41	6.0	Hong Kong	45	7.3
Japan	113	4.8	Saudi Arabia	31	4.6	Netherlands	44	7.2
Switzerland	66	2.8	Egypt	28	4.1	South Korea	37	6.0
Nigeria	58	2.5	Germany	28	4.1	France	27	4.4
India	56	2.4	Netherlands	27	4.0	Japan	23	3.8
Nipah	Frequency	% $N = 382$	Lassa	Frequency	% $N = 285$			
USA	186	48.7	USA	123	43.2			
Malaysia	88	23.0	Germany	74	26.0			
Australia	66	17.3	France	34	11.9			
Bangladesh	29	7.6	Nigeria	32	11.2			
France	25	6.5	Sierra Leone	19	6.7			
Canada	23	6.0	Guinea	17	6.0			
Japan	19	5.0	Canada	15	5.3			
Germany	17	4.5	UK	12	4.2			
Singapore	16	4.2	Netherlands	10	3.5			
UK	15	3.9	Belgium	9	3.2			
			Japan	9	3.2			

SARS Severe acute respiratory syndrome, *MERS* Middle East respiratory

Sweileh WM. Global Health. 2017 Feb 8;13(1):9.

Epidemiyoloji: Nijerya Güncel Durum

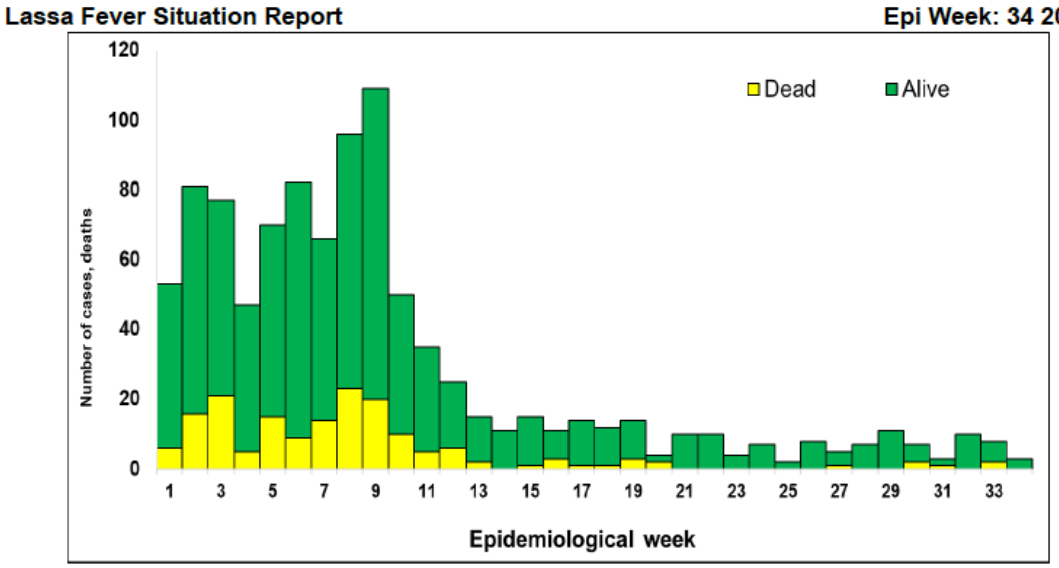


Figure 1. Confirmed Lassa Fever Cases in Nigeria Epidemiological Week 34, 2024

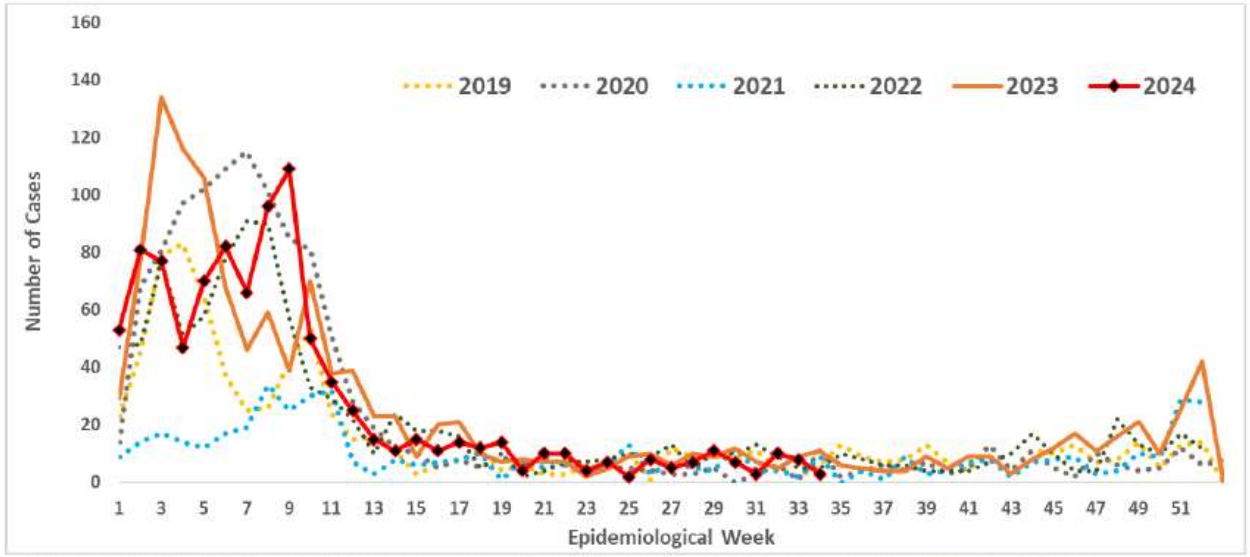


Figure 6: Trend of confirmed cases by epidemiological week, 2019– 2024, Nigeria

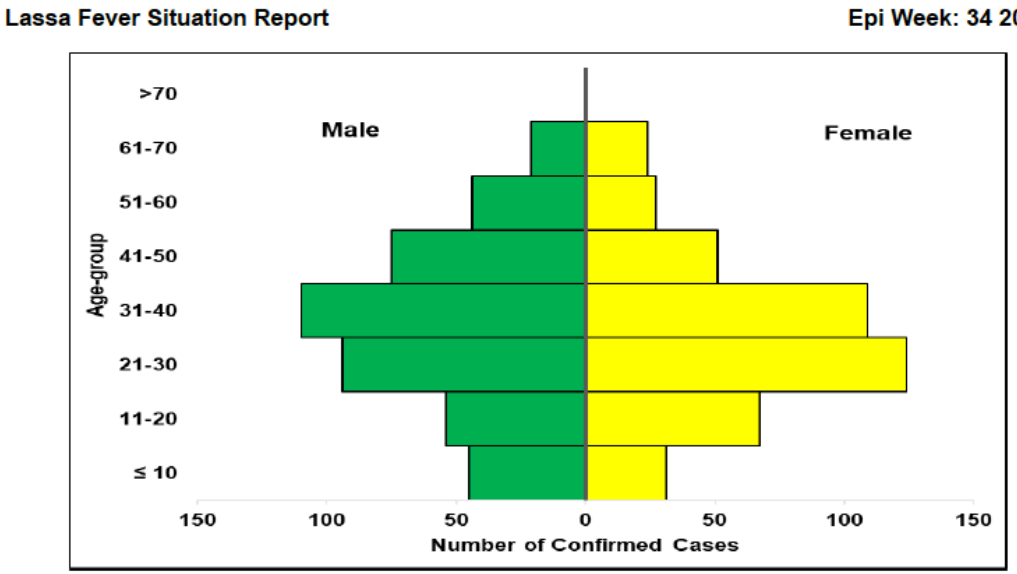


Figure 4. Age and sex pyramid showing the number of confirmed Lassa fever cases for 2024

https://ncdc.gov.ng/diseases/sitreps/?cat=5&name=An%20update%20of%20Lassa%20fever%20outbreak%20in%20Nigeria

Bulaşma Yolları

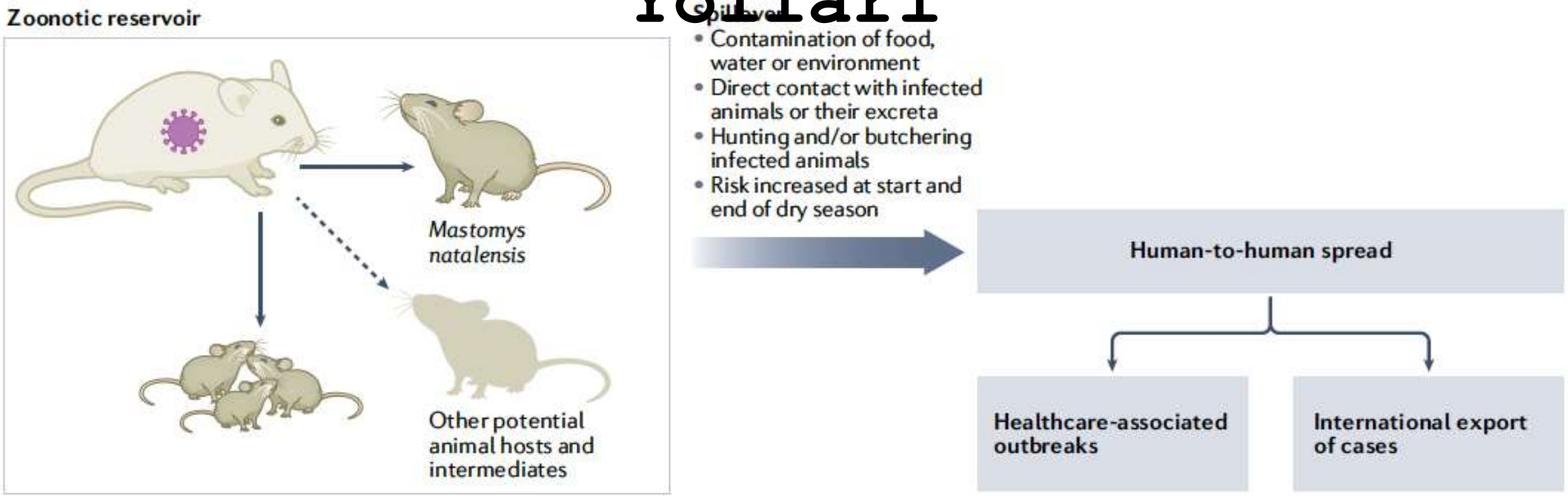


Fig. 2 | **Lassa virus transmission.** The major reservoir of Lassa virus (LASV) is *Mastomys natalensis*. LASV spreads among *Mastomys* via horizontal or vertical (congenital) routes. Other animal species can also be infected with LASV. Spillover of LASV occurs by exposure to excretions of *Mastomys* or intermediate hosts, or during preparation of infected animals for food. Human-to-human transmission can occur in the home or clinical setting.

Garry RF. Lassa fever - the road ahead. Nat Rev

Bulaşma Yolları

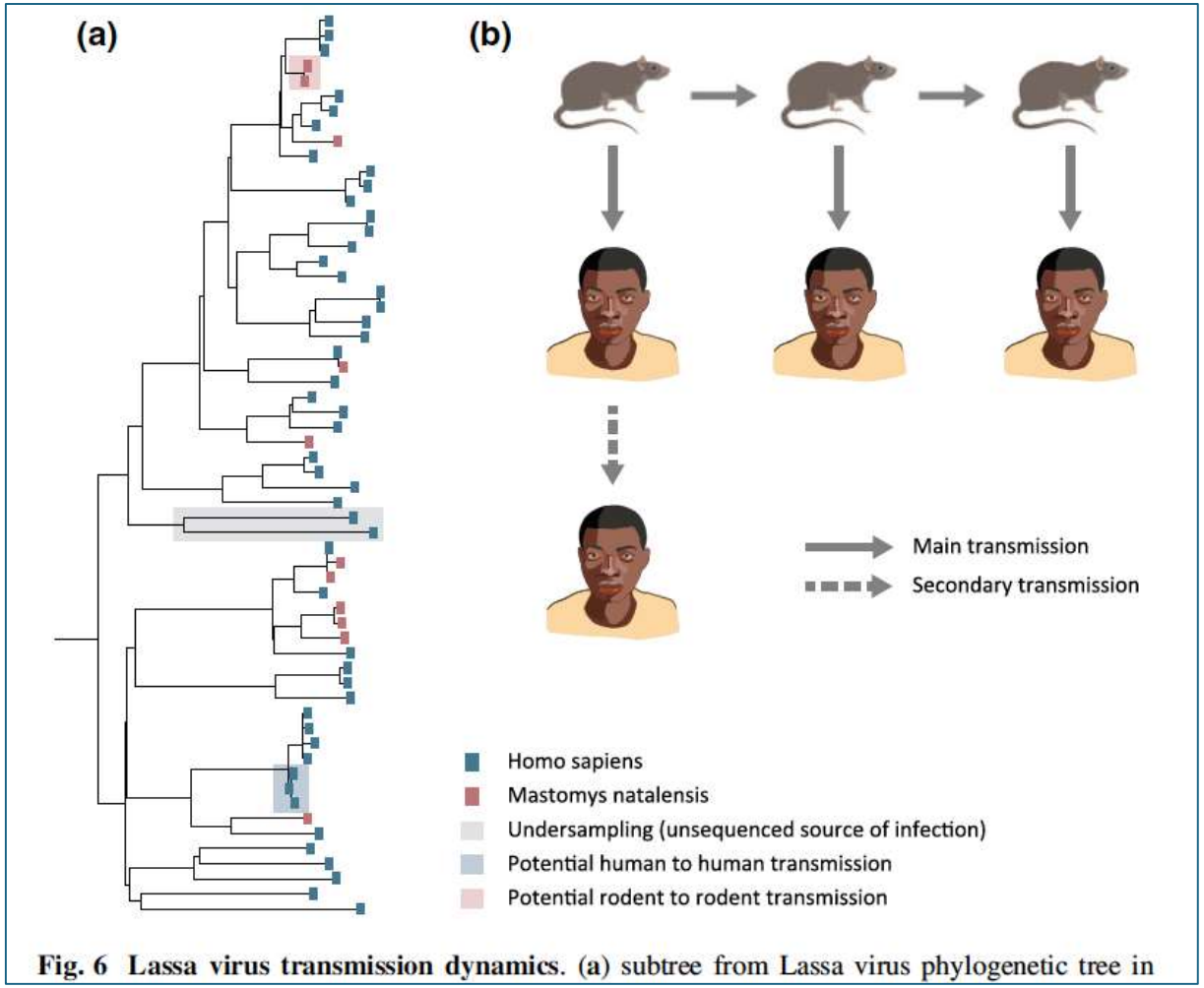
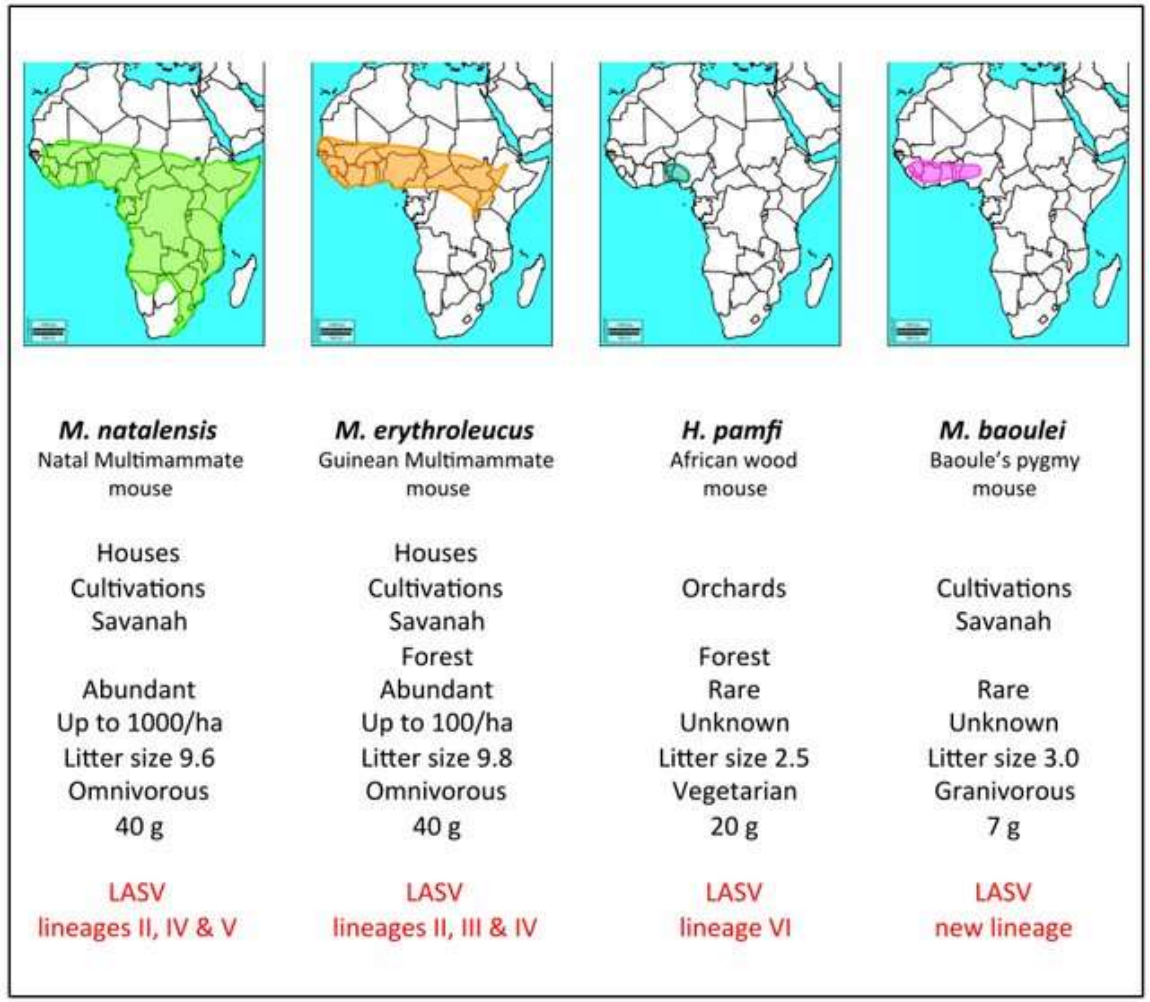


Fig. 6 Lassa virus transmission dynamics. (a) subtree from Lassa virus phylogenetic tree in



Robert Garry. Lassa feve

Klinik Özellikler

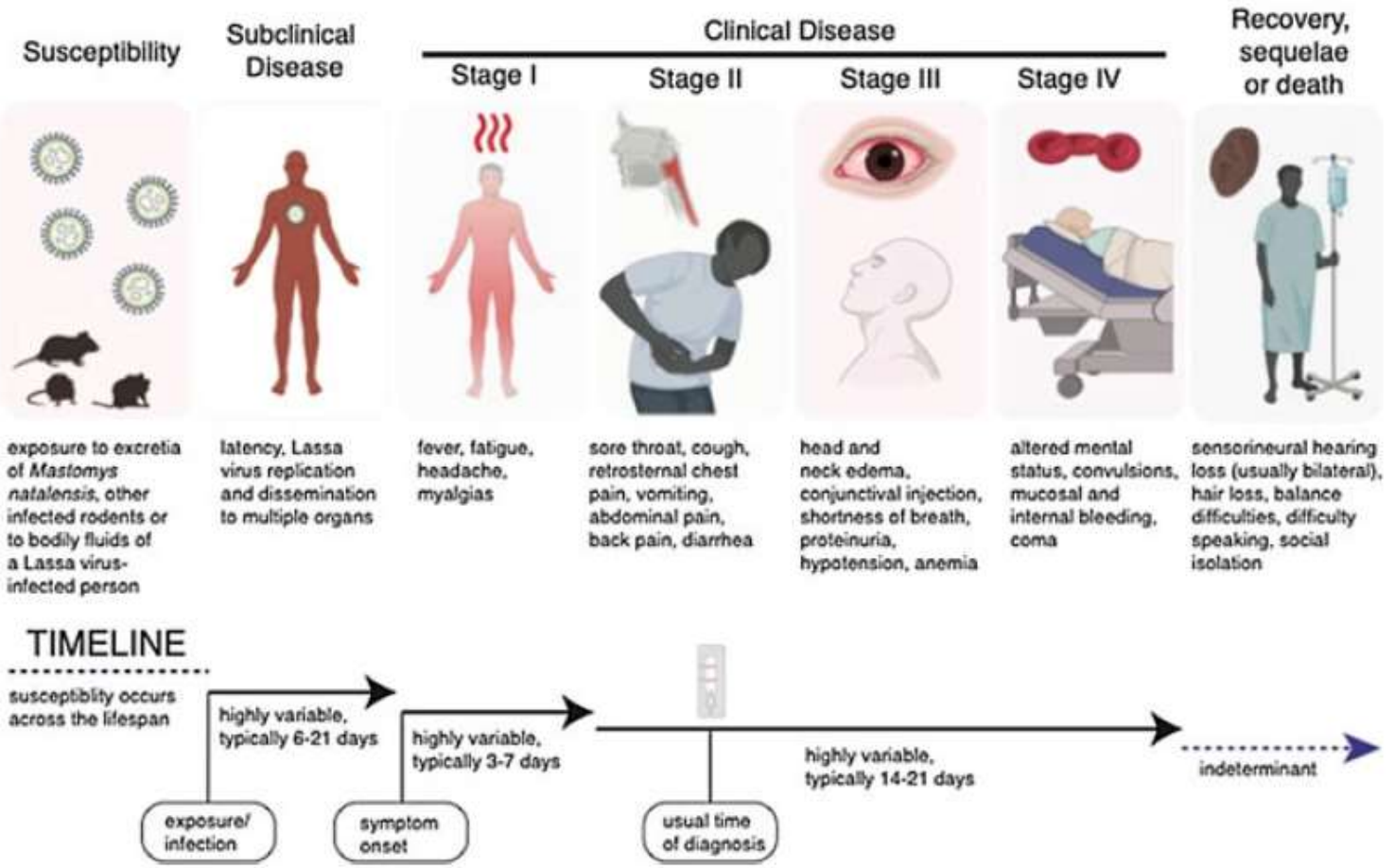
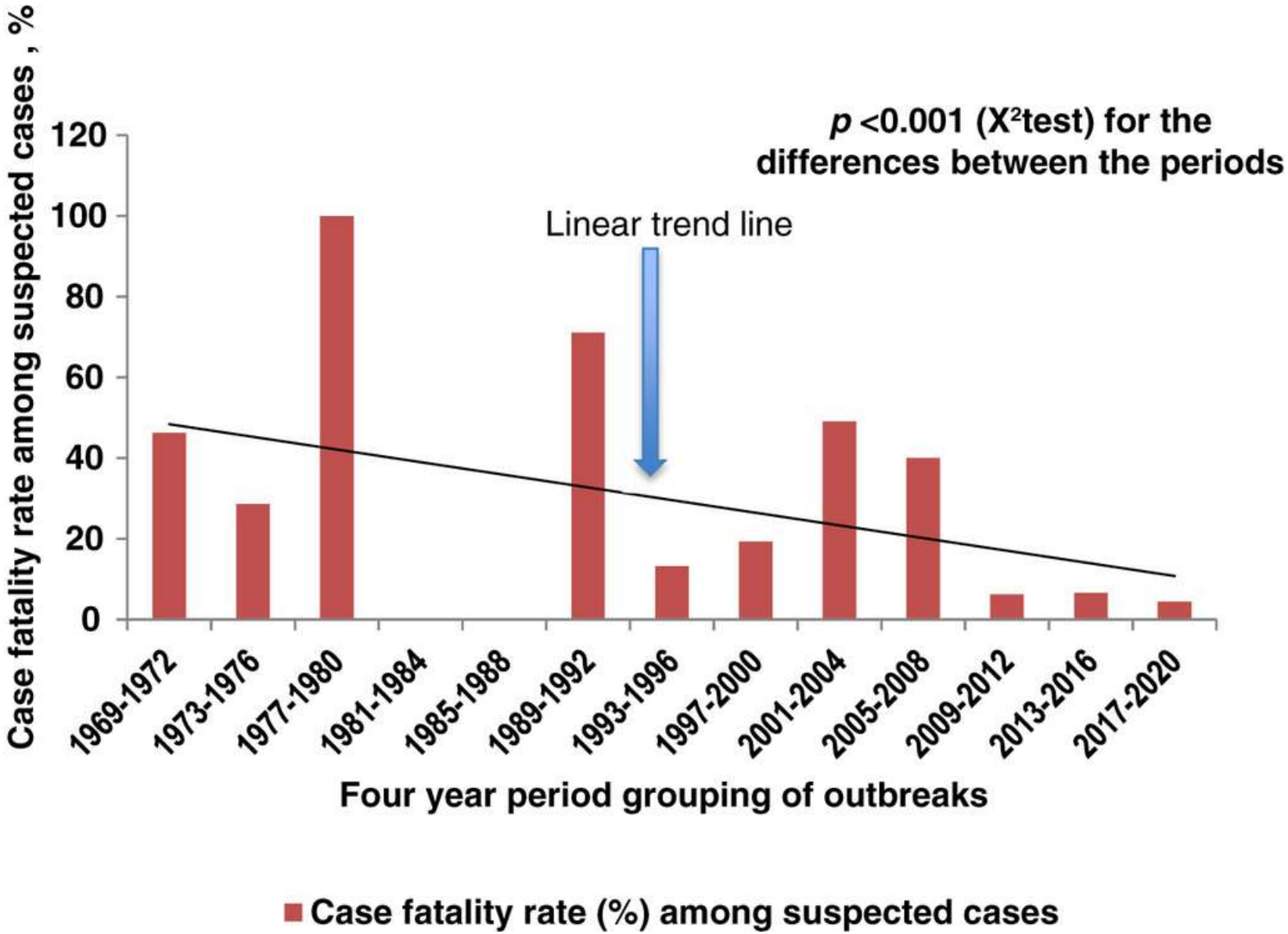


Fig. 1 Natural history of Lassa fever. Lassa fever is a zoonotic infection that has a variable clinical course. After a prolonged but highly variable latency phase, patients may present a spectrum of illnesses. Stages in clinical severity are associated with a variety of signs and symptoms. The major sequelae of Lassa fever typically involve auditory deficits

Robert Garry. Lassa feve



Mortalite: %1
Yatan hastada mortalite: %15

Agbonlahor DE, et al.52 Years of Lassa Fever Outbreaks in Nigeria, 1969-2020. Am J Trop Med Hyg. 2021;105(4):974-985.

Klinik Özellikler: Komplikasyonları

Box 4: Complications of Lassa fever?

High likelihood, short term complications

- Spontaneous abortion and fetal mortality in pregnant women

Medium likelihood, long term complications

- Deafness (sensorineural)—Seen in approximately 25% of patients who survive the disease and can be permanent[15]

Low likelihood, long term complications

- Neuropsychiatric sequelae—Includes sleep disturbance, psychosis, hallucinations, and depression[33]
- Transient hair loss
- Gait disturbance
- Polyserositis

Houlihan C. BMJ. 2017 Jul 12;358:j2986.

Klinik Özellikler: Prognoz Faktörleri

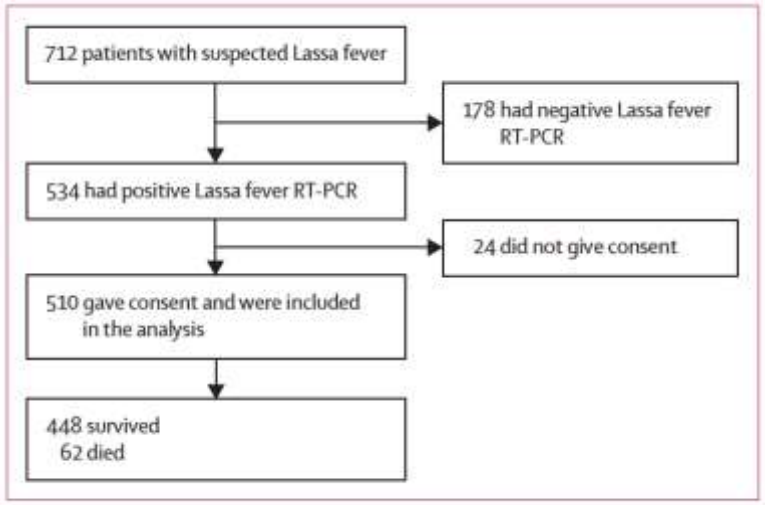
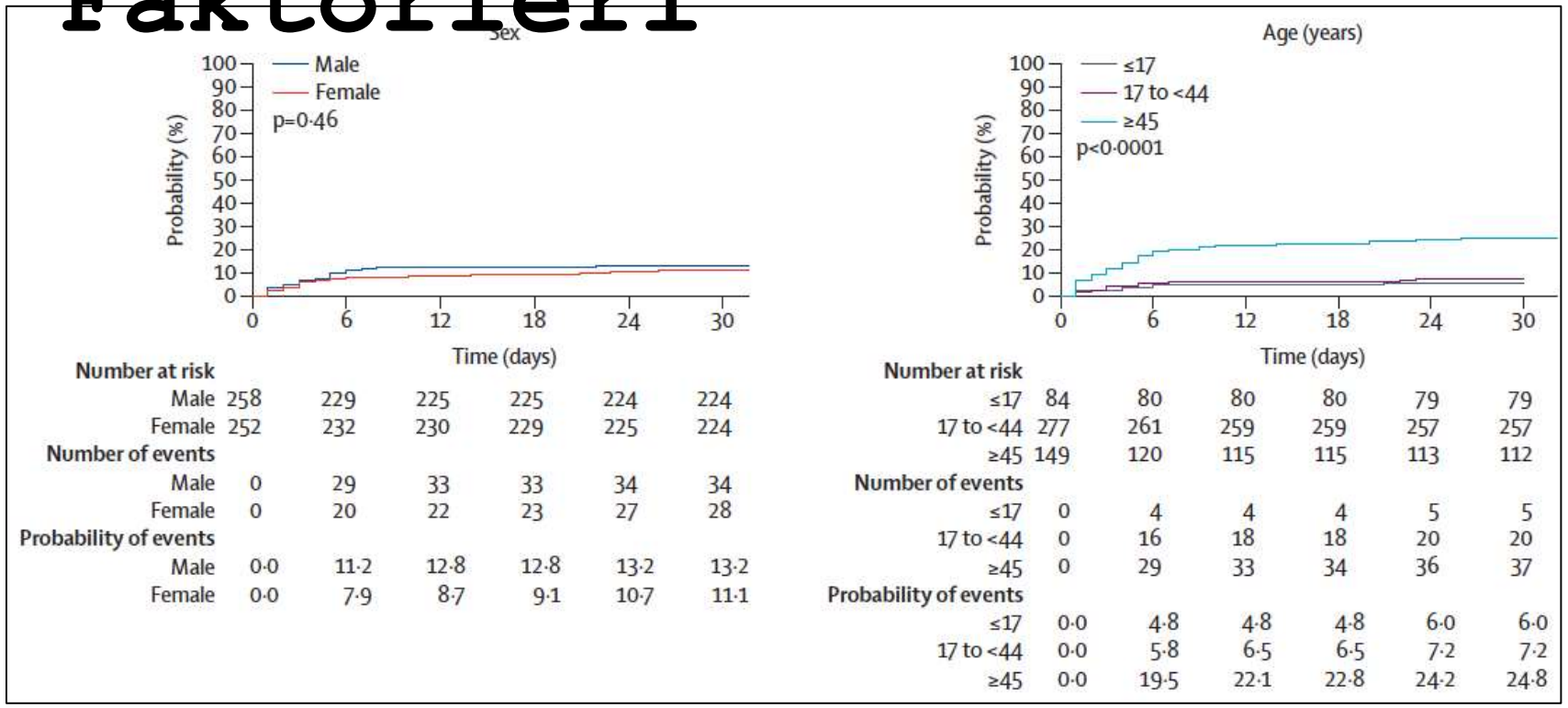
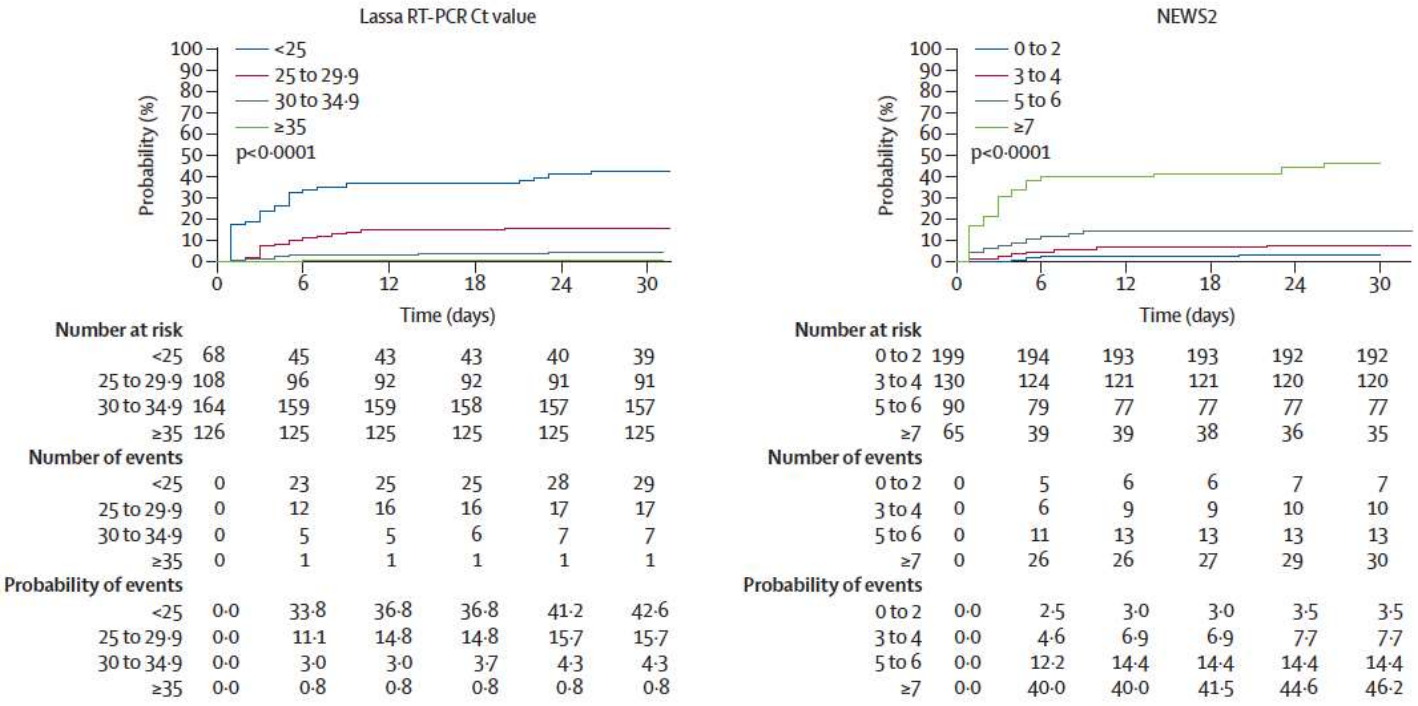
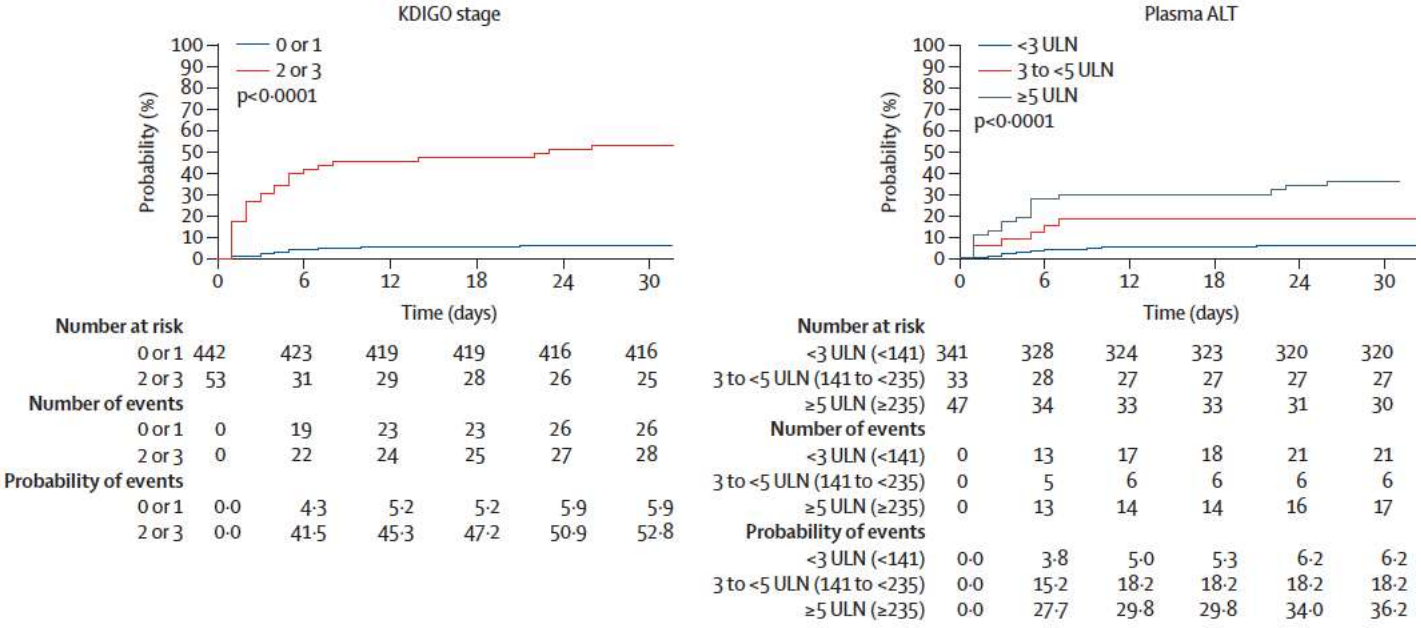


Figure 1: Flow chart of participants



Duvignaud A, Lassa fever outcomes and prognostic factors in Nigeria (LASCOPE): a prospective cohort





62 (%12) hasta öldü. (57 [%13] erişkin ve [%6] çocuk). Ölüme kadar geçen süre 3 gün (ortanca)

	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

Data are n (%) unless otherwise specified. ALT=alanine aminotransferase. Ct=cycle threshold (GPC gene as a target). KDIGO=Kidney Disease-Improving Global Outcome. NEWS2=National Early Warning Score, second version. ULN=upper limit of normal range.

***Table 3*: Association between mortality and baseline characteristics, multivariable analysis (n=377)**

Duvignaud A, Lassa fever outcomes and prognostic factors in Nigeria (LASCOPE): a prospective cohort

Poor Prognostic Indicators

- High viral load and viremia
- Grossly abnormal liver function tests (high AST levels)
- Renal failure (high urea and creatinine)
- Severe bleeding
- Encephalitis
- Third trimester pregnancy
- Generalized edema

Asogun DA, et al. Infect Dis Clin North Am. 2019

Tanı

- RT-PCR testi
- ELISA testi

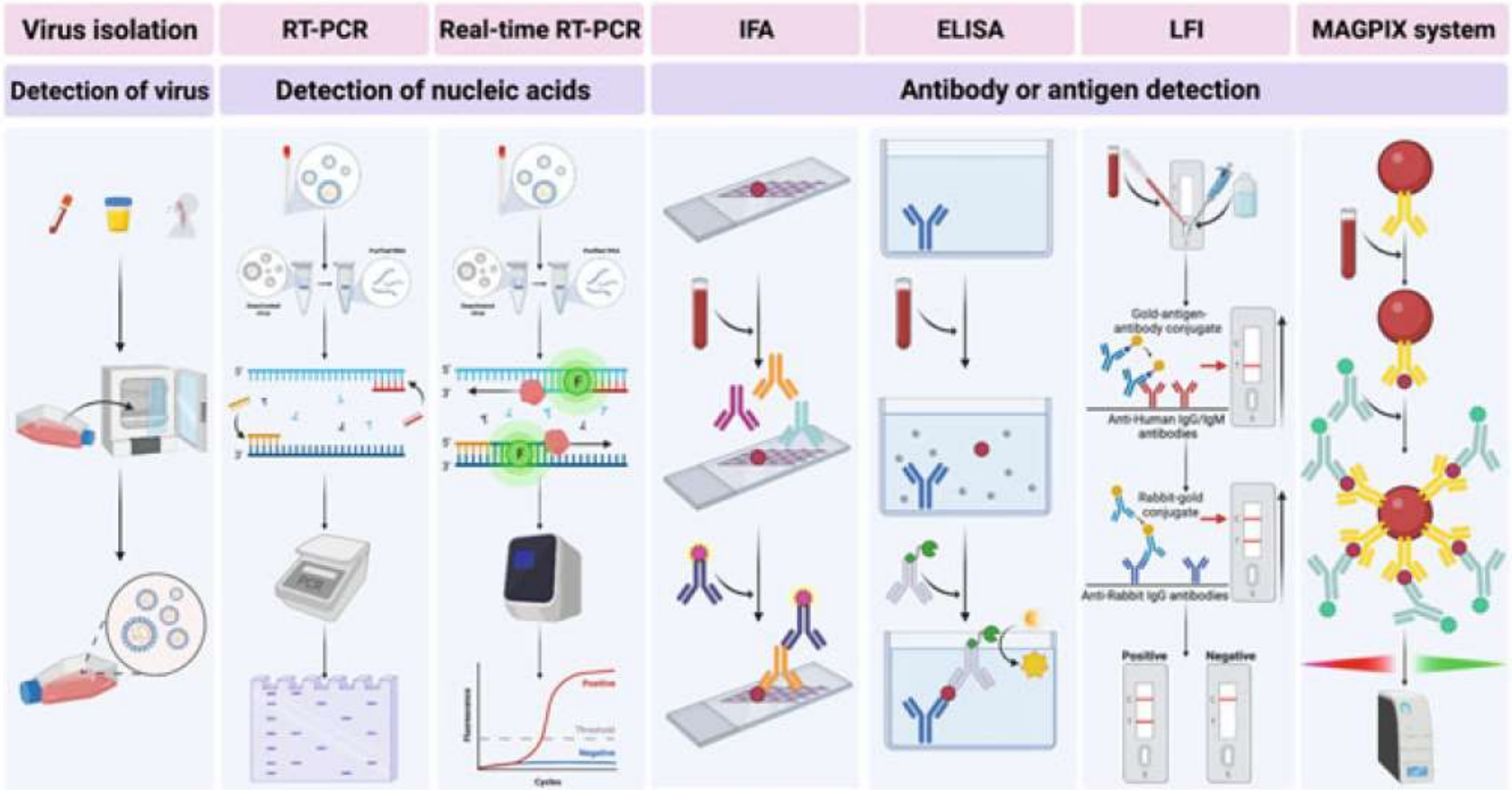
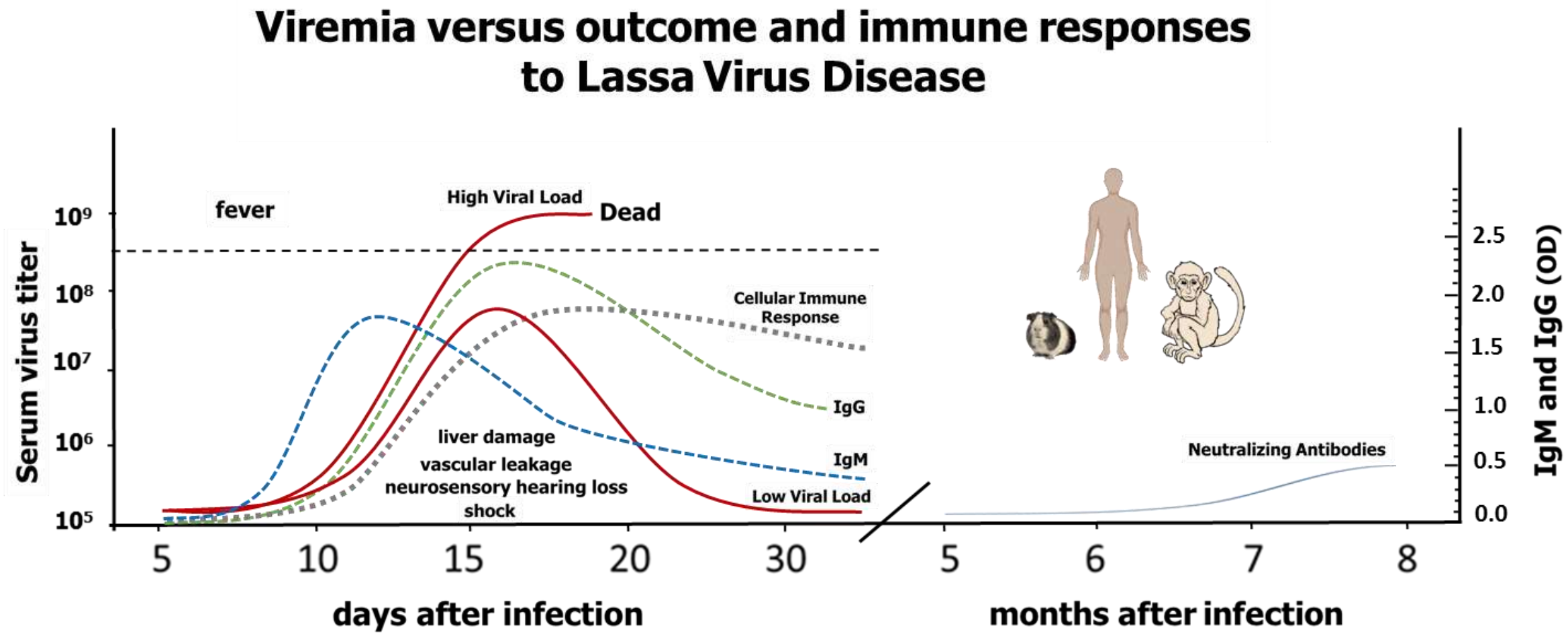


Fig. 1 LASV diagnostics. LASV diagnostics are based on the detection of virus (virus isolation), detection of nucleic acids (RT-PCR and real-time RT-PCR), and detection of antibody or antigen (IFA, ELISA, LFI, and MAGPIX system). Steps of each diagnostic method are depicted above. Created with BioRender.com

Robert Garry. Lassa feve

Tan1



Zapata et al. *Pathogens* **2018**, *7*(4), 84

Tanı: Laboratuvar ve Radyoloji

Box 2: Possible further investigations

- *Renal function and serum electrolytes*—Moderately elevated creatinine has been seen in patients with Lassa fever, probably indicating dehydration or damage from elevated creatine kinase[14]
- *Blood lactate or arterial blood gases*—Blood lactate, arterial or venous pH, and bicarbonate can be used to indicate tissue hypoperfusion and guide fluid management in patients with Lassa fever
- *Full blood count*—An elevated haematocrit is seen, usually indicative of dehydration. Thrombocytopenia has been described[20]
- *Coagulation studies*—Coagulation should be measured and corrected as necessary
- *Liver function tests*—Elevated alanine transaminase levels have been noted and associated with worse outcome[21]
- *Chest x ray*—A chest x ray should be done to look for pleural or pericardial effusion
- *Urine analysis*—Urine analysis should be done to screen for proteinurea
- *Blood cultures*—Blood cultures may be helpful in the identification of other causes of sepsis (such as deep abdominal infection, upper urinary tract infection, endocarditis, or discitis)
- *Lumbar puncture*—Encephalopathy is quite common among symptomatic patients who present after more than six days of symptoms. However, detection of Lassa virus RNA in cerebrospinal fluid has been rarely reported, since lumbar puncture risks healthcare worker exposure and is unlikely to alter the management of patients with confirmed Lassa fever.[16]
- *Ultrasonography*—Could be considered for the investigation of intraperitoneal fluid and pericardial effusion[22]

Houlihan C. BMJ. 2017 Jul 12;358:j2986.

Ayırıcı Tanı

- **Ebola virüs hastalığı:** Benzer şekilde ateş, titreme, kusma, ishal ve genel ağrı semptomları görülür. İç ve dış kanamalar da olabilir.
- **Sıtma:** Akut ateş, baş ağrısı ve bazen ishal semptomları görülebilir.
- **Tifo:** Ateş, baş ağrısı, döküntü, gastrointestinal semptomlar, lenfadenopati ve göreceli bradikardi görülebilir.
- **Sarı humma ve diğer Flaviviridae virüsleri:** Hemorajik komplikasyonlar görülebilir.
- **Şigelloz:** İshal, ateş, bulantı ve bazen toksemi, kusma ve kramplar görülebilir.
- **Viral hepatit**
- **Leptospiroz**
- **Romatizmal ateş**

Tedavi

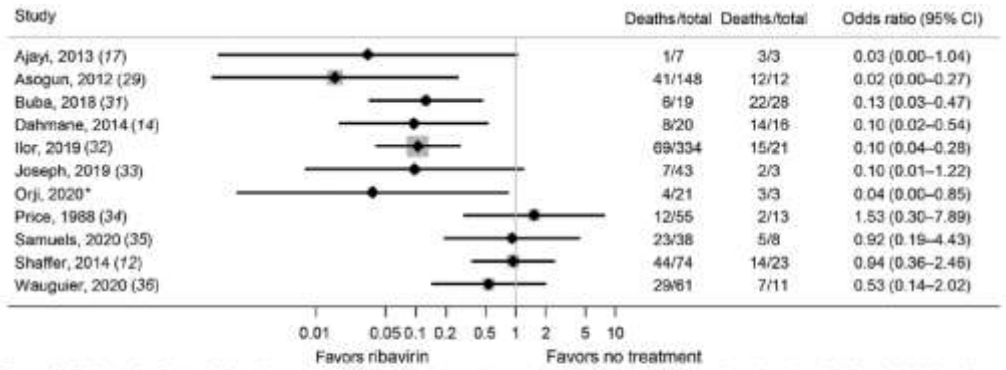


Figure 4. Estimated effects of ribavirin compared with no treatment on mortality outcomes from studies other than McCormick (*11*) and IND 16666 (Birch & Davis Associates and Shenkon Inc., US Army Medical Research and Development Command, unpub. data, https://media.tghn.org/medialibrary/2019/03/Responsive_Documents_of_Peter_Horby.pdf.pdf, G.V. Ludwig, pers. comm., 2019 March 4, https://media.tghn.org/medialibrary/2019/03/Dr._Ludwig_memo.pdf) studies in a systematic review of published and unpublished studies for evidence for ribavirin treatment of Lassa fever. *M.-L. Orji et al., unpub. data, https://doi.org/10.20944/preprints202005.0269.v1. A horizontal line represents the 95% CI of a study result, with each end of the line representing the boundaries. A point estimate of the study result is represented by a black diamond. A gray box gives a representation of the size of a study compared with all studies in the figure.

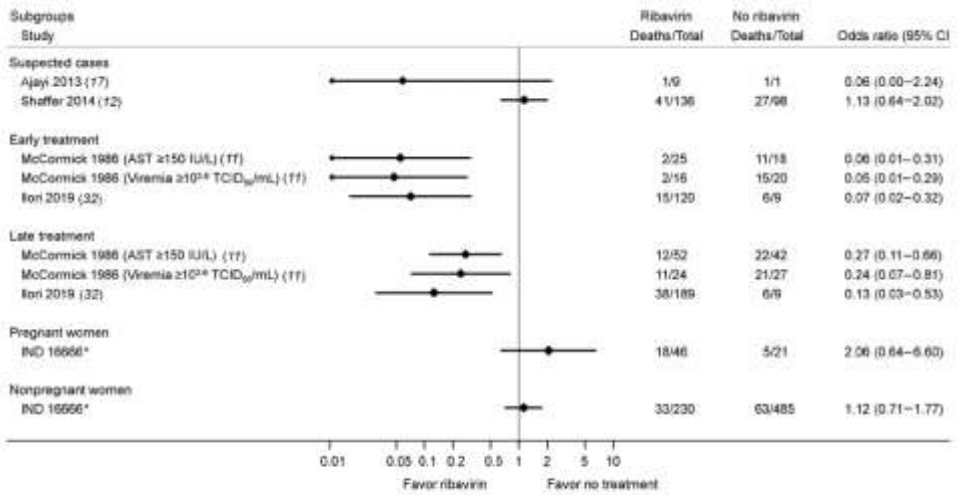
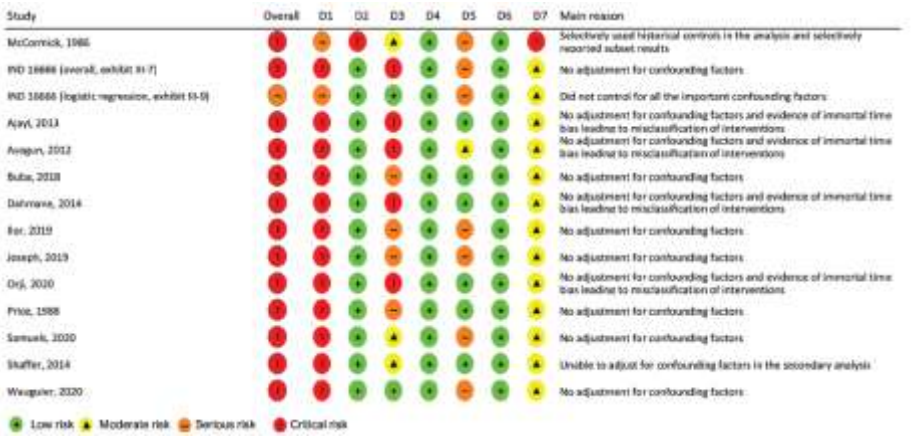


Figure 5. Estimated effects of ribavirin compared with no treatment on mortality outcomes within patient subgroups in a systematic review of published and unpublished studies for evidence for ribavirin treatment of Lassa fever. *IND 16666, unpublished study requested by P.W.H. through the US Freedom of Information Act (Birch & Davis Associates and Shenkon Inc., US Army Medical Research and Development Command, unpub. data, https://media.tghn.org/medialibrary/2019/03/Responsive_Documents_of_Peter_Horby.pdf.pdf, G.V. Ludwig, pers. comm., 2019 March 4, https://media.tghn.org/medialibrary/2019/03/Dr._Ludwig_memo.pdf)

Lack of Evidence for Ribavirin Treatment of Lassa Fever in Systematic Review of Published and Unpublished Studies[1]

Hung-Yuan Cheng, Clare E. French, Alex P. Salam, Sarah Dawson, Alexandra McAleenan, Luke A. McGuinness, Jelena Savović, Peter W. Horby, Jonathan A.C. Sterne



Cheng HY et al. Lack of Evidence for Ribavirin Treatment of Lassa Fever in Systematic Review of Published and Unpublished Studies. Emerg Infect Dis. 2022 Aug;28(8):1559-1568

3.2.1A Adults including non-pregnant adults (McCormick regimen)

Period	Dose	Frequency
Loading Dose	33mg/kg (maximum dose of 2.64 g)	Stat
Day 1-4	16mg/kg (maximum dose of 1.28 g)	6 hourly
Day 5-10	8mg/kg (maximum dose of 0.64g)	8 hourly

**For patients who require dialysis, give IV ribavirin 4 hours before dialysis session*

3.2.1B Adults including non-pregnant adults (Irrua regimen)

Period	Dose	Frequency
Loading Dose	100mg/kg (maximum of 7g)	In 2 divided doses: 2/3 given stat & 1/3 given 8 hours later
Day 2-7	25mg/kg	Daily (single dose)
Day 8-10	12.5 mg/kg	Daily (single dose)

Day two commences 24 hours after first component of the loading dose and subsequent daily dose follow same dosing pattern

3.3.1 ISTH Regimen for Pregnant women (Modified McCormick regimen)

Management of Lassa fever in Pregnant women is carried out using the modifie McCormick Regimen, irrespective of the gestational age of the pregnancy

Period	Dose	Frequency
Loading Dose (Day 1)	100mg/kg	In 2 divided doses. 2/3rd of loading dose given sta and after 8 hours, remaining 1/3rd is given
Day 2-5	16mg/kg	6 hourly
Day 6-10	8mg/kg	8 hourly

For a pregnant woman who weighs 70kg, total calculated dose will be 7000mg. 2/3rd of the total calculated dose (4700mg) will be given stat and balance of 2300mg given 8 hours later). From day 2-5, total calculated daily dose will be 1120mg given 6 hourly and from Day 6-10, total calculated daily dose will be 560mg given 8hourly

OA-652

SAFETY AND TOLERABILITY OF FAVIPIRAVIR FOR THE TREATMENT OF LASSA FEVER: A RANDOMIZED CONTROLLED OPEN LABEL PHASE II CLINICAL TRIAL

[1,6]Mirjam Groger*, [2]Kevin Okwaraeke, [3,8]Peter Akhideno, [5,6]Meike Pahlmann, [4]Christine Kleist, [1]Cédric Mbavu, [5,6]Julia Hinzmann, [1]Veronika Schlicker, [3]Femi Babatunde, [5,6]Ndapewa Ithete, [3]Osahogie Edeawe, [1]Francisca Sarpong, [9,10,12]Camille Fritzell, [9,11,12]Alexandre Duvignaud, [9,11,12]Denis Malvy, [3,7]Sylvanu Okogbenin, [9,10,12]Marie Jaspard, [4]Sebastian Wicha, [5]Stephan Günther, [1,6]Michael Ramharter, [2]Oluwafemi Ayodeji, [3,8]Cyril Erameh. *[1]Department of Tropical Medicine, Bernhard Nocht Institute for Tropical Medicine and I. Department of Medicine University Medical Center Hamburg-Eppendorf, Germany; [2]Infection Control and Research Centre, Federal Medical Centre Owo, Nigeria; [3]Institute of Lassa Fever Research and Control, Irrua Specialist Teaching Hospital; [4]Department of Clinical Pharmacy, Institute of Pharmacy, University of Hamburg, Germany; [5]Department of Virology, Bernhard Nocht Institute for Tropical Medicine, Germany; [6]German Center for Infection Research (DZIF), Hamburg-Lübeck-Borstel-Riems, Germany; [7]Department of Obstetrics and Gynecology, Irrua Specialist Teaching Hospital, Nigeria; [8]Department of Medicine, Irrua Specialist Teaching Hospital, Nigeria; [9]Univ. Bordeaux, Inserm 1219, IRD 271, Bordeaux Population Health, France; [10]The Alliance for International Medical Action, Senegal; [11]Department of Infectious Diseases and Tropical Medicine, Division of Tropical Medicine and Clinical International Health, CHU de Bordeaux, Hôpital Pellegrin, France; [12]Programme PAC-CI/ANRS Research Site, Côte d'Ivoire*

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Human-monoclonal-antibody therapy protects nonhuman primates against advanced Lassa fever

Chad E Mire[1,2,11], **Robert W Cross**[1,2,11], **Joan B Geisbert**[1,2], **Viktoriya Borisevich**[1,2], **Krystle N Agans**[1,2], **Daniel J Deer**[1,2], **Megan L Heinrich**[3], **Megan M Rowland**[3], **Augustine Goba**[4,5], **Mambu Momoh**[4,5,6], **Mathew L Boisen**[3], **Donald S Grant**[4,5], **Mohamed Fullah**[4,5,10], **Sheik Humarr Khan**[4,5,10], **Karla A Fenton**[1,2], **James E Robinson**[7], **Luis M Branco**[3,11], **Robert F Garry**[3,8,9], and **Thomas W Geisbert**[1,2]

Önleme

One Health

A multisectorial approach in understanding how humans, animals and the environment influence emergence of diseases

Environment

Variations in climate and land perturbations

Humans

Frequent interactions with animals and their habitat

Animals

Role of wild and domestic animals in disease emergence

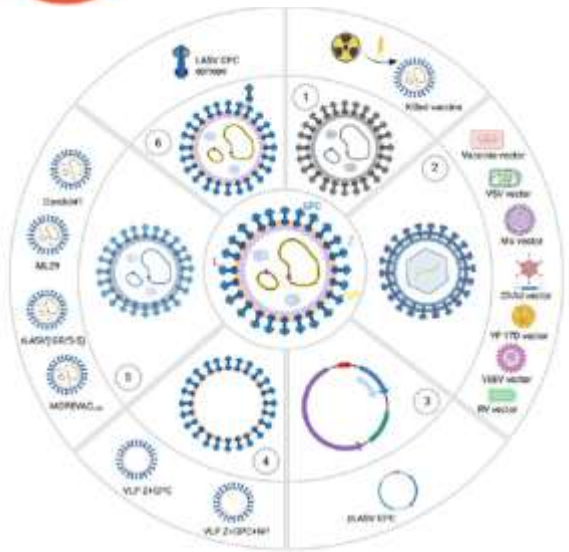
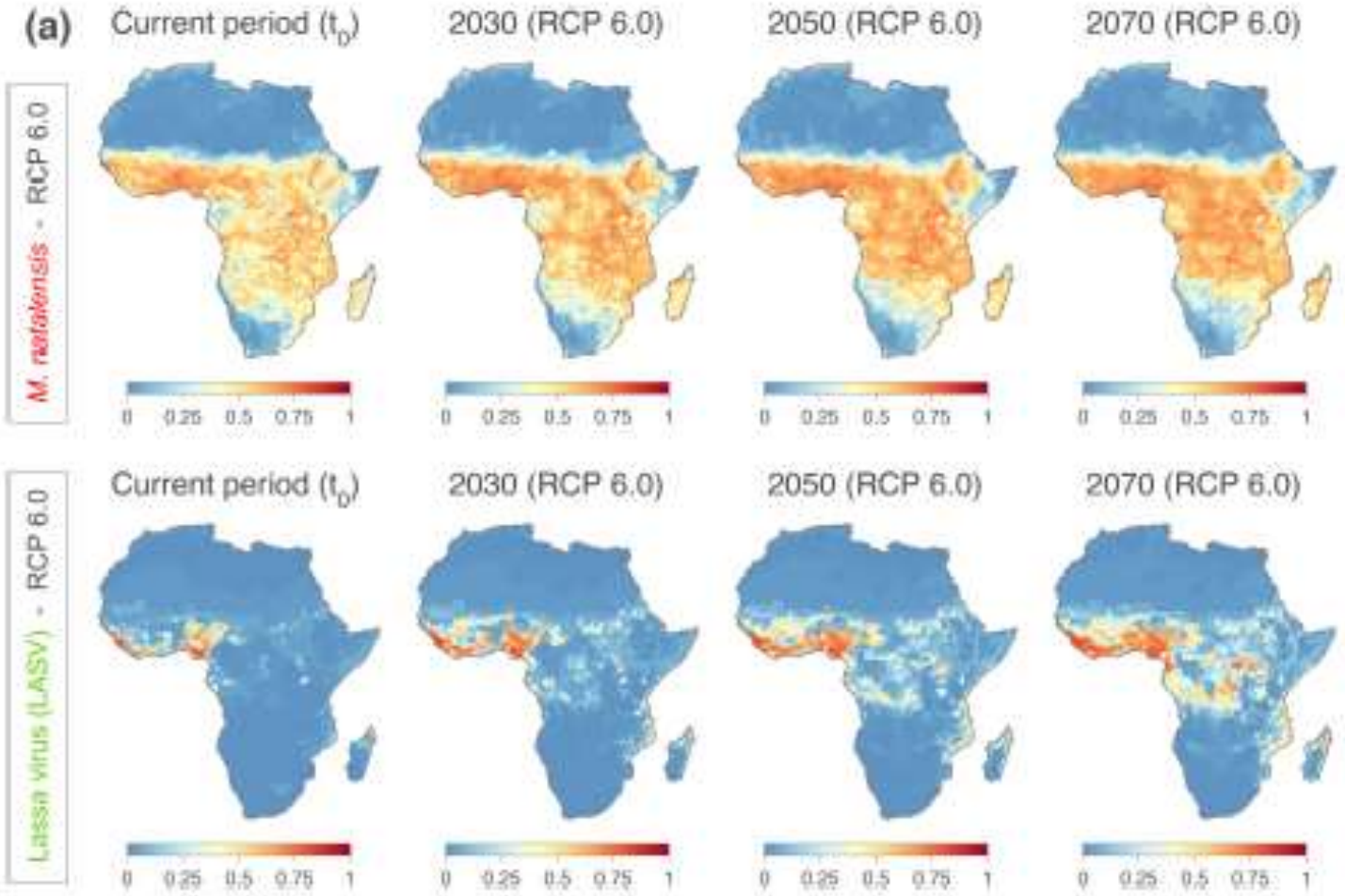


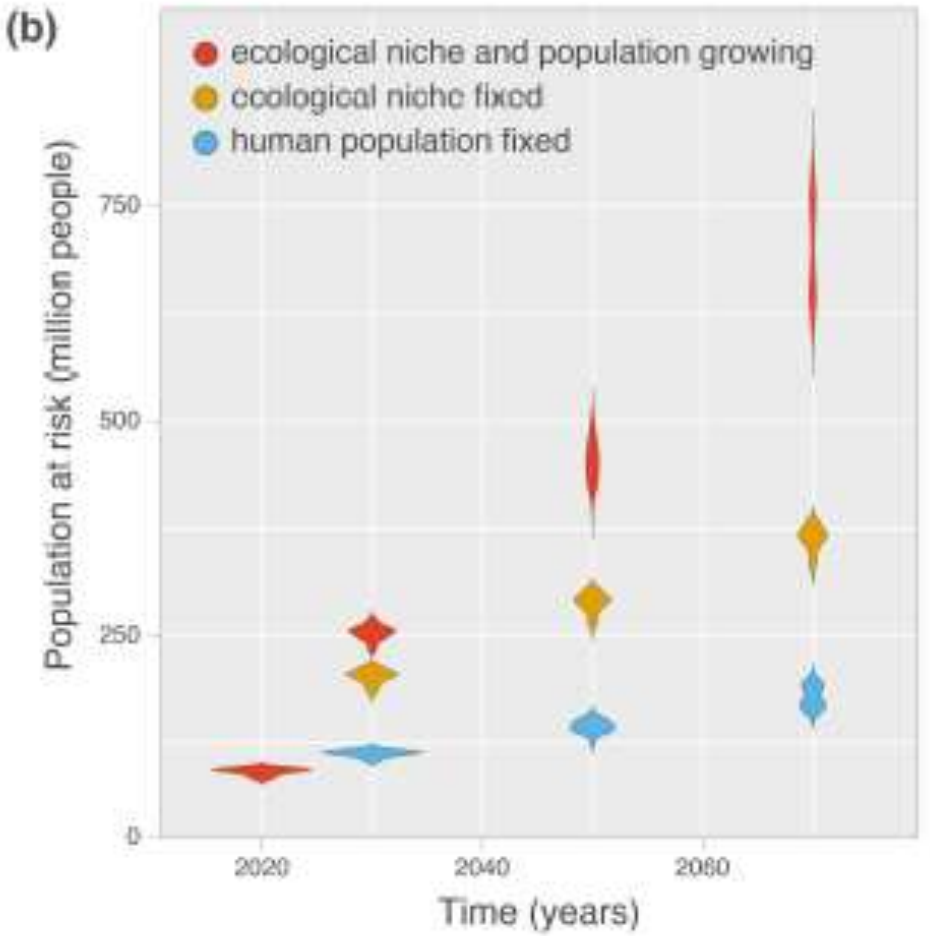
Fig. 3 LASV vaccines. LASV vaccines include inactivated vaccines, virus vector vaccines, DNA vaccines, VLP vaccines, live-attenuated vaccines, and epitope vaccines. Created with BioRender.com

Türkiye’de Lassa Ateşi

- Türkiye'de şu ana kadar Lassa ateşi vakası bildirilmedi.
- Lassa ateşi virüsünün taşıyıcısı olan *Mastomys natalensis* Türkiye’de bulunmamaktadır.
- Bu nedenle, hastalığın Türkiye'de doğal olarak ortaya çıkma riski oldukça

Lassa Ateşi Pandemiye Yol Açabilir mi?





Klitting R et al. Nat Commun. 2022

Lassa Ateşi Pandemiye Yol Açabilir mi?

- Lassa ateşinin küresel bir salgına yol açma potansiyeli düşük olsa da, tamamen göz ardı edilemez.
  - Sınırlı Yayılma Potansiyeli
  - Lassa ateşi şu anda Batı Afrika'da endemiktir ve çoğunlukla bu bölgeyle sınırlıdır.
  - İnsandan insana bulaşma nadirdir ve genellikle enfekte kişilerin vücut sıvılarıyla doğrudan temas gerektirir.
  - Virüsün ana rezervuarı olan Mastomys cinsi kemirgenler Batı Afrika dışında yaygın değildir.
- Küresel Yayılma Riskleri
  - Artan uluslararası seyahat, enfekte kişilerin diğer ülkelere seyahat etme olasılığını artırır.
  - İnkübasyon uzun ve asemptomatik klinik durum riski artırıyor.
  - Sağlık sistemleri zayıf olan ülkelerde salgınlar kontrol edilemeyebilir.

Lassa Ateşi Virüsü: Biyoterörizm Pot

Agents/Diseases

- Anthrax (*Bacillus anthracis*)
- Botulism (*Clostridium botulinum* toxin)
- Plague (*Yersinia pestis*)
- Smallpox (variola major)
- Tularemia (*Francisella tularensis*)
- Viral hemorrhagic fevers, including
  - Filoviruses (Ebola, Marburg)
  - Arenaviruses (Lassa, Machupo)

Lassa fever research priorities: towards effective medical countermeasures by the end of the decade

Kristine A Moore, Julia T Ostrowsky, Angela J Mehr, Rebecca A Johnson, Angela K Ulrich, Nicolina M Mova, Petra C Fay, Peter J Hart, Josephine P Golding, Virginia Benassi, Marie-Pierre Preziosi, Ifedayo M Adetifa, George O Akpede, William K Ampofo, Danny A Asogun, Alan D T Barrett, Daniel G Bausch, Ilse de Coster, Devy M Emperador, Heinz Feldmann, Elisabeth Fichet-Calvet, Pierre B H Formenty, Robert F Garry, Donald S Grant, Stephan Günther, Swati B Gupta, Marie Jaspard, Laura T Mazzola, Sylvanus A Okogbenin, Cathy Roth, Connie S Schmaljohn, Michael T Osterholm

https://emergency.cdc.gov/agent/agentlist-category.asp

Kristine A Moore et al. Lancet Infect Dis, July 1, 2024

OpenWHO hosts courses on 9 WHO priority diseases