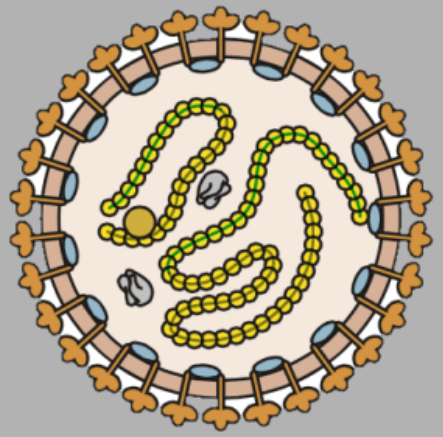

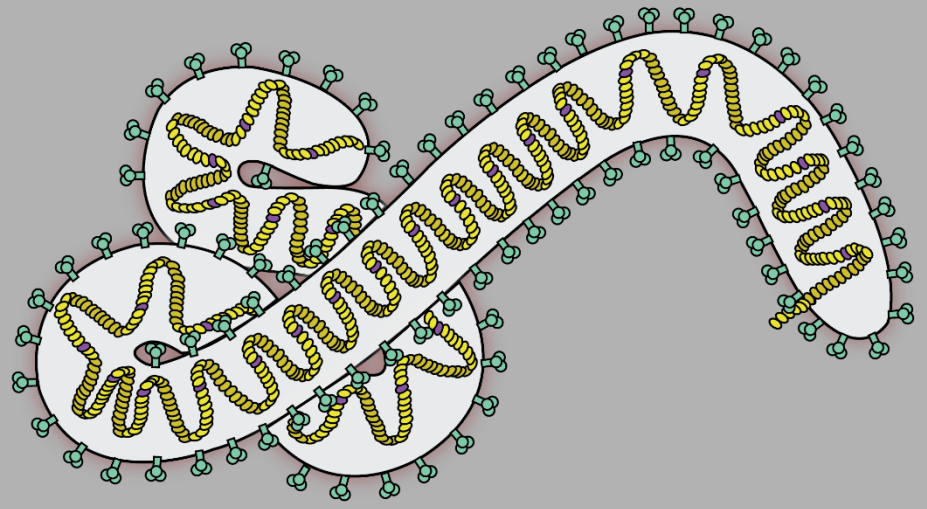

VACCINES FOR VIRAL HEMORRHAGIC FEVERS : UPDATE

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Center for viral emerging disease, Division of Tropical and humanitarian medicine
HUG

VIRAL HEMORRHAGIC FEVERS

Viral hemorrhagic fevers (VHFs) are a heterogeneous group of diseases that are caused by over 30 viruses from 4 distinct families of viruses:

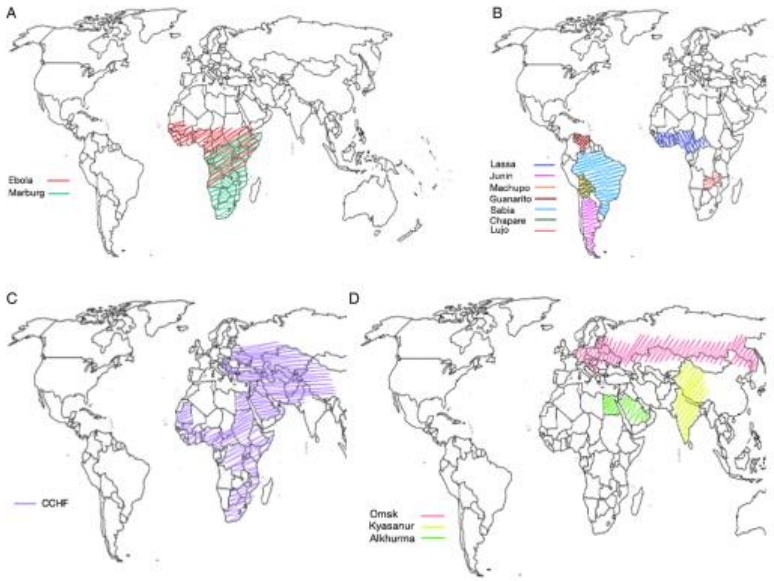


Figure 1 (A) Map of *Filoviridae* viral haemorrhagic fever (VHF). (B) Map of *Arenaviridae* viral haemorrhagic fever. (C) Map of *Bunyaviridae* viral haemorrhagic fever. (D) Map of *Flaviviridae* viral haemorrhagic fever.

Family	Vectors	Disease
Arenaviridae	Rodent	Lujo virus fever Lassa fever Argentine, Bolivian and Venezuelan fever
Filoviridae	Bats	Ebola virus disease Marburg virus disease
Flaviviridae	Mosquito* Tick*	Dengue fever, Yellow fever Omsk fever Kyasanur forest disease
Bunyaviridae	Mosquito* Tick* Rodent	Rift valley fever Crimean-Congo hemorrhagic fever Hantavirus fever

* Arbovirosis and zoonosis : vertebrates, monkeys

VIRAL HEMORRHAGIC FEVERS

Characteristics

- All RNA virus
- Start as a non specific febrile illness
- Some VHFs cause relatively mild illness, while others can cause severe, life threatening disease, might include bleeding, or hemorrhaging
- Most VHFs have no known cure or vaccine

Human to human transmission

- Ebola virus disease +++
- Marburg virus disease +++
- Crimean-Congo hemorrhagic fever ++
- Lassa fever +

- Impact on preventive measures and outbreak control

WHO PRIORITY DISEASES IN EMERGENCY CONTEXTS - 2018

Accelerated Research & Development based on

… potential to cause a public health emergency

… absence of efficacious drugs and/or vaccines

- Crimean-Congo hemorrhagic fever
- Ebola virus disease and Marburg virus disease
- Lassa fever
- Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS)
- Nipah and henipaviral diseases
- Rift Valley fever
- Zika
- "Disease X" *Disease X represents the knowledge that a serious international epidemic could be caused by a pathogen currently unknown to cause human disease*

https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts

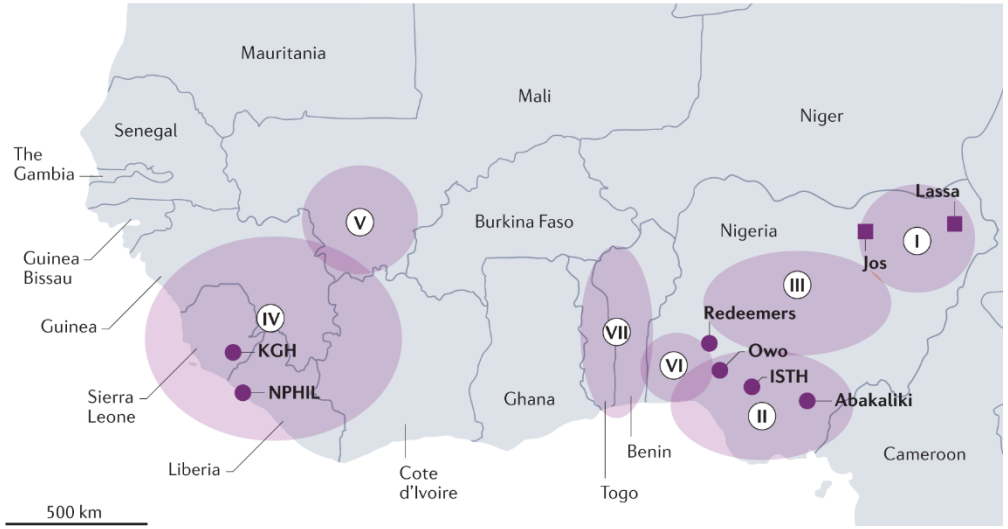
LASSA FEVER

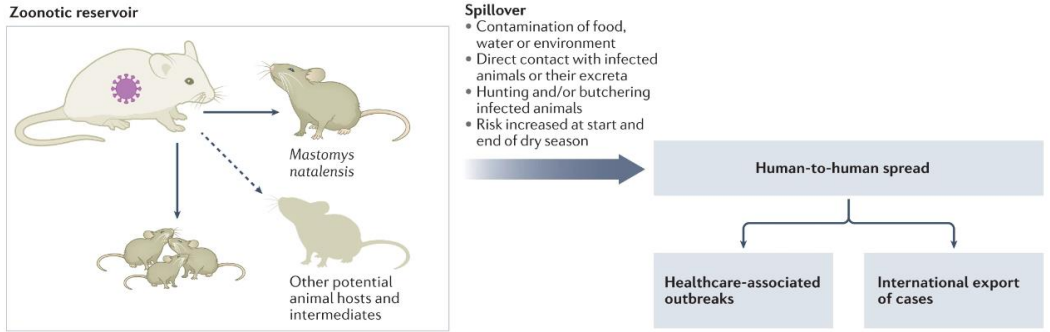
Epidemiology

- Discovered in 1969. Endemic in Benin, Ghana, Guinea, Liberia, Sierra Leone, Mali, Togo and Nigeria (sporadic and outbreaks)
- 100'000-300'000 cases/year, underreported, up to 50% seroprevalence in SL and Guinea, ~5'000 deaths/year

Virus

- Lassa virus (LASV), family: *Arenaviridae*
- 7 genetic lineages (I-VII)
- Zoonosis → main reservoir: peridomestic multimmate rodent : *Mastomys natalensis* (bushmeat)
- Tranmission: exposure to food or household items contaminated with urine and faeces of infected rats
  - Rodent to human 80%, Human to human 20%





LASSA FEVER

Disease

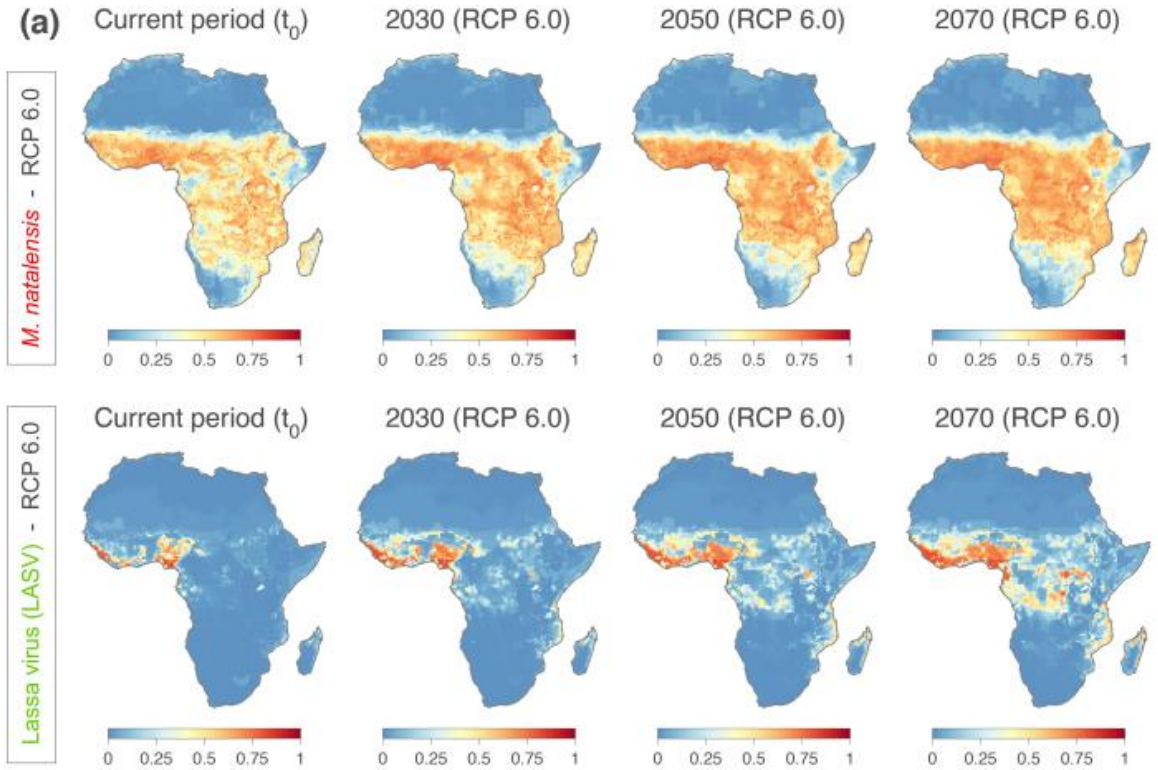
- Incubation 2-21 days
- Gradual onset, aspecific presentation
  - Asymptomatic (subclinic) 80%
  - Complications in severe cases: increased vascular permeability, hypovolemic shock and multiorgan failure
- CFR 1%, up to 80% in pregnant women/fetus 3rd trimester, higher in hospitalized setting
- Neurological sequelae : 34%
  - memory loss, ataxia, neuromuscular discomfort and sensorineural hearing loss
- Supportive care

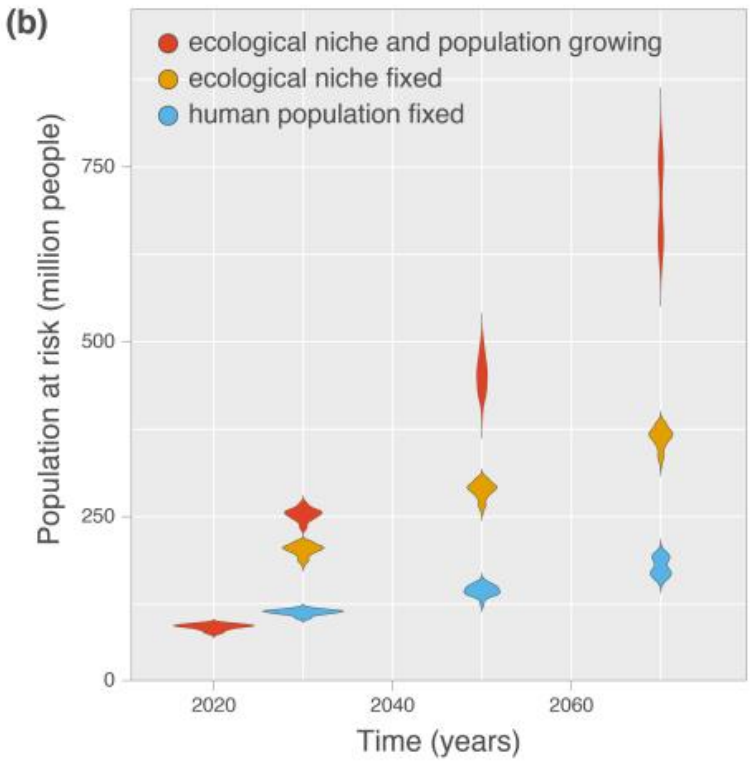
Public health impact

- Among all VHFs : largest global disease burden after Dengue fever
- ~60 million people at risk in endemic regions
  - Increased in the frequency and size of outbreaks (ongoing in Nigeria)
- Data on incidence lacking
- At-risk population
  - Infection/outbreak in health care settings
  - Imported cases (travel-associated)
  - High mortality in pregnant women
- Neurological sequelae in survivors

THE HUMAN POPULATION AT RISK FOR LASSA FEVER LIKELY TO EXPAND

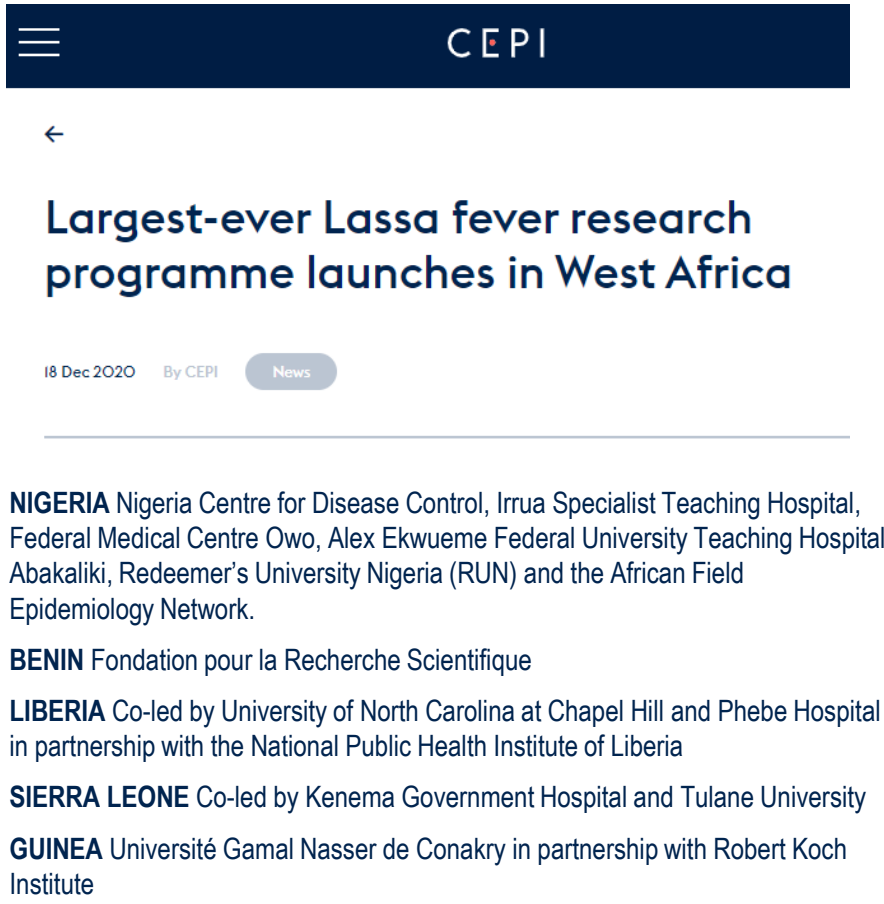
Projected ecological niche suitability of Mastomys natalensis and Lassa virus, as well as human population at risk of exposure to Lassa Virus





Klitting Nature 2022

ENABLE LASSA RESEARCH PROGRAM (CEPI), DEC 2020



CEPI

Largest-ever Lassa fever research programme launches in West Africa

18 Dec 2020 By CEPI News

NIGERIA Nigeria Centre for Disease Control, Irrua Specialist Teaching Hospital, Federal Medical Centre Owo, Alex Ekwueme Federal University Teaching Hospital Abakaliki, Redeemer's University Nigeria (RUN) and the African Field Epidemiology Network.

BENIN Fondation pour la Recherche Scientifique

LIBERIA Co-led by University of North Carolina at Chapel Hill and Phebe Hospital in partnership with the National Public Health Institute of Liberia

SIERRA LEONE Co-led by Kenema Government Hospital and Tulane University

GUINEA Université Gamal Nasser de Conakry in partnership with Robert Koch Institute

Up to 23,000 participants enrolled in Benin, Guinea, Liberia, Nigeria and Sierra Leone

US 26 million in funding

Aims:

- Number of infection
- Differences in age and gender of people getting infected
- Accurate overview on the proportion of asymptomatic and symptomatic cases.

https://cepi.net/news_cepi/largest-ever-lassa-fever-research-programme-launches-in-west-africa/

VACCINE DEVELOPMENT FOR LASSA FEVER

2 scenarios:

1. Non-emergency setting (preventive use)
   - Protection of populations living in areas where Lassa virus is endemic
     - Suitable for pregnant women
     - All age groups
   - HCWs, laboratory personnel, deployed international workers
2. Emergency setting (reactive/outbreak use)
   - Protection of at-risk persons in the area of ongoing outbreak for the prevention of LF as well as interruption of chains of virus transmission
   - Usefull in large outbreak in new/unexpected setting with extensive HHT

Accelerating the licensure of Lassa vaccines: Generating robust evidence on vaccine efficacy and safety

25 – 26 October 2022

Date: Tuesday 25 October, 2022 & Wednesday 26 October, 2022

Location: Abuja, Nigeria

Hybrid Meeting: In-person & Online

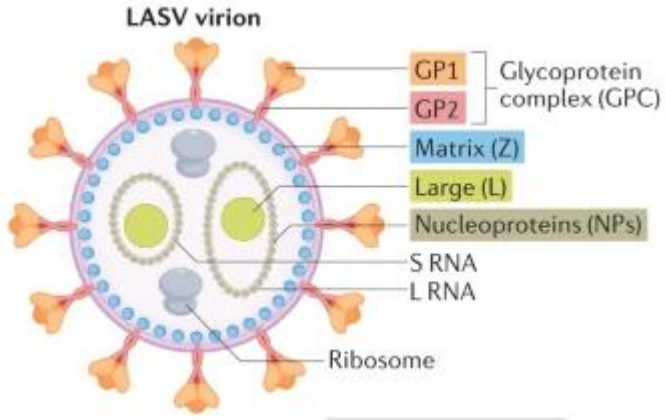
The WHO R&D Blueprint Team and Coalition for Epidemic Preparedness Innovations (CEPI) together with the co-hosting partner organisations Nigeria Centre of Disease Control (NCDC) and Africa Centres for Disease Control and Prevention (ACDC), are organising a workshop on "Accelerating the licensure of Lassa vaccines Generating robust evidence on vaccine efficacy and safety".

https://www.who.int/news-room/events/detail/2022/10/25/default-calendar/save-the-date---accelerating-the-licensure-of-lassa-vaccines--generating-robust-evidence-on-vaccine-efficacy-and-safety

OPTIMAL CANDIDATES FOR LASSA FEVER VACCINE

- Safety/reactogenicity comparable to WHO recommended routine vaccination
  - No neurological complications associated with LF
- Single dose regimen (without requirement for a booster)
- At least 90% (70%) efficacy in preventing infection/disease caused by **LASV lineages I-IV**
- Long lasting immunity (≥ 5 years, min 1 year)
- Injectable (im, sc, id), monodose, maximal volume 0.5ml
- Shelf life at least 5 years at 2-8°C
- Co-administration with other vaccines licensed for the same age

- Challenges
  - Multiples lineages
  - Possible immune mediated complication in survivors → sensorineural hearing loss
  - Cellular immunity more effective in clearing LASV infection compared to humoral immunity



https://www.who.int/news-room/events/detail/2022/10/25/default-calendar/save-the-date---accelerating-the-licensure-of-lassa-vaccines--generating-robust-evidence-on-vaccine-efficacy-and-safety

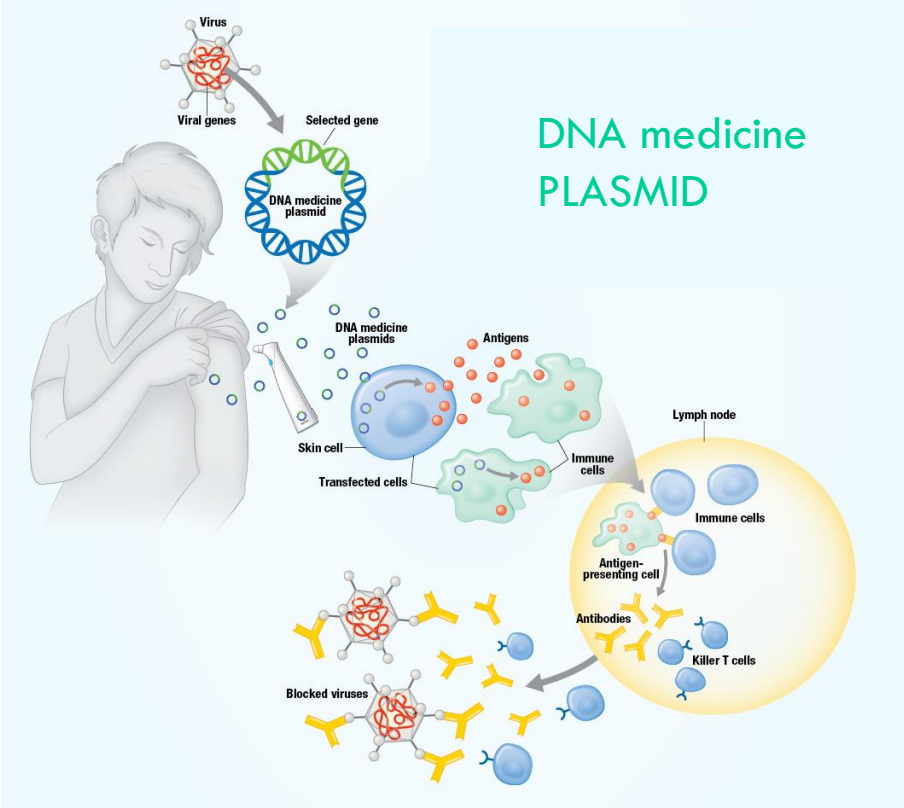
LASSA FEVER VACCINE CANDIDATES

INO-4500 (INOVIO/CEPI)

- Optimized DNA plasmid encoding GPC lineage IV (Josiah strain)
- 2 dose regimen
- ID (//mantoux) followed be ID electroporation
- Generate cellular and immune response in animal models

- Vaccine immunogenicity demonstrated in animal models
- Vaccine efficacy demonstrated in NHPs
  - Protection up to 1 year
  - No hearing loss (in NHPs)
- Cross-reactivity against lineages 1- IV, VII

- LSV 001 Phase 1 (safety, tolerability and immunogenicity) completed in Oct 2022 (US)
  - 40/20 participants, No safety concerns, no related SAEs
- LSV 002 Phase 1b completed in Sept 2022 (Ghana)
  - 176/44 participants, No safety concerns, no related SAEs, met target immune response
- LSV 201 Phase 2a in West Africa: in planning, all age group



https://www.inovio.com/dna-medicines-pipeline/

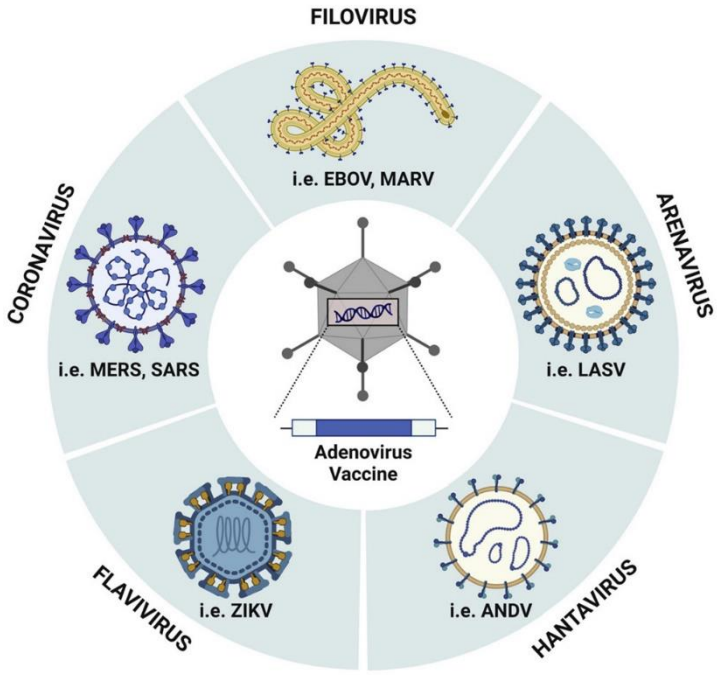
LASSA FEVER VACCINE CANDIDATES

ChAd0x1-Lassa-GPC (University of Oxford)

- Non replicating simian adenoviral vectored vaccine encoding the GPC lineage IV (Josiah strain)
  - No pre-existing immunity (simian Ad)
- Induced strong cellular and humoral immune responses after single dose
- Suitable for large scale, low cost manufacture
  - Can be stored at 2-8°C for at least 6 months
- Single or prime-boost delivery

- Vaccine efficacy demonstrated in guinea pigs (homologous challenge)
- Cross-reactivity (lineage I-III) demonstrated in mice, GP challenge
- Vaccine efficacy demonstrated in NHPs

- In planning Phase 1 studies:
  - Phase 1a : UK
  - Phase 1b : West Africa



Fischer RJ. NPJ Vaccines 2021

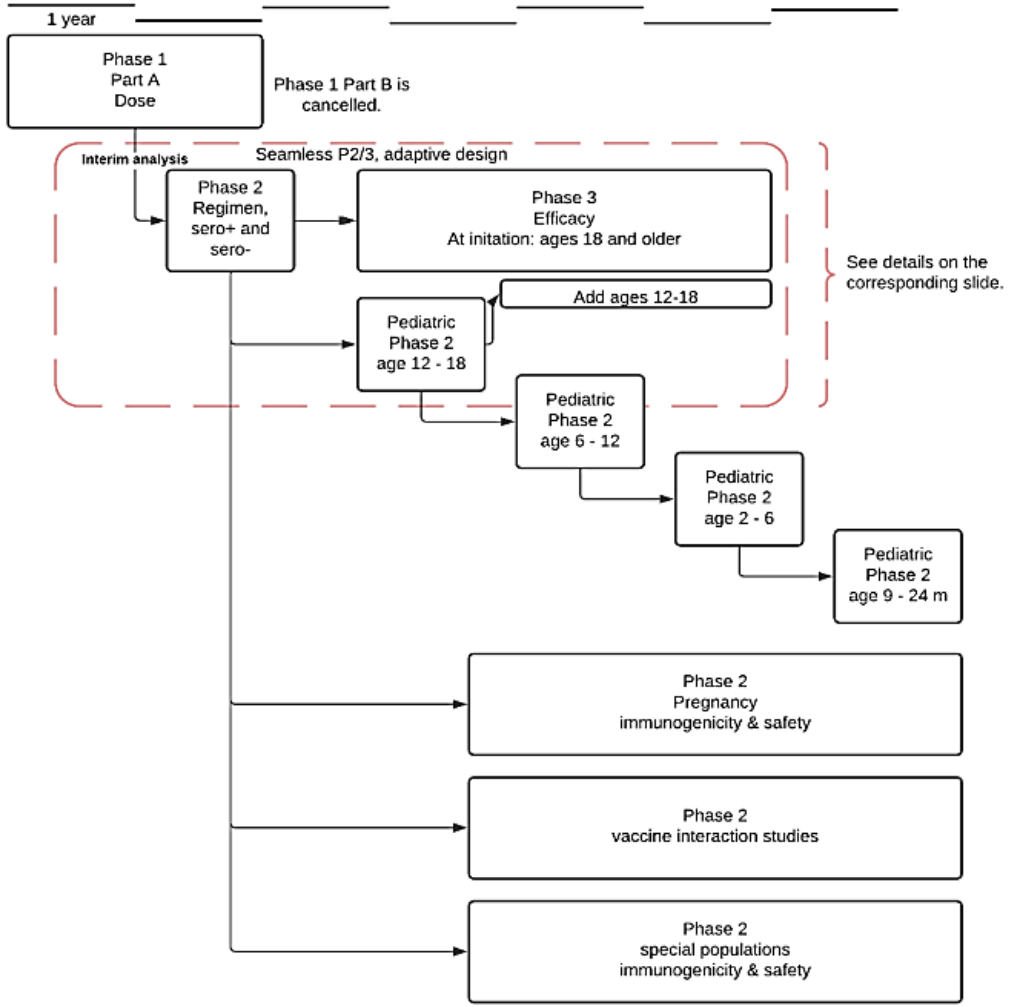
LASSA FEVER VACCINE CANDIDATES

EBS-LASV (EMERGENT/CEPI)

- rVSV vectored vaccine encoding the GPC lineage IV (Josiah strain)
- Possible long term storage at -20°C and at least 6 months at 4°C
- Single dose regimen, im

- Vaccine efficacy demonstrated in NPHs
- Cross-efficacy for lineage II in NPHs

- Phase 1 studies initiated in Ghana
- In planning innovative adaptive phase 2/3 studies in West Africa



https://www.emergentbiosolutions.com/products-services/pipeline/

LASSA FEVER VACCINE CANDIDATES

rVSVΔG-LASV-GPC (IAVI/CEPI multiple partners)

- Replication-competent, recombinant viral vector encoding the GPC lineage IV (Josiah strain)
- Single dose delivery, im
- Vaccine efficacy demonstrated in NHPs
  - Protection up to 1 year
- Cross-neutralization demonstrated in NHPs (lineage I-III, VII)
- Protection as soon as 3 days after vaccination (lethal challenge)

- Phase 1 study US : No related SAEs, no hearing loss, <2 days of symptoms
  - Liberia: ongoing
- Phase 2a study (safety & tolerability) ongoing in Sierra Leone, Liberia and Nigeria. *Healthy adults, children, HIV+*
- Phase 2b study (dose-ranging) ongoing in Sierra Leone, Liberia and Nigeria
- Future phase 2b/3 study (safety & efficacy) in Sierra Leone, Liberia and Nigeria

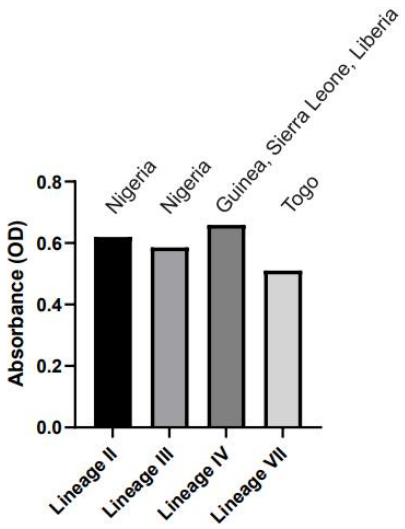
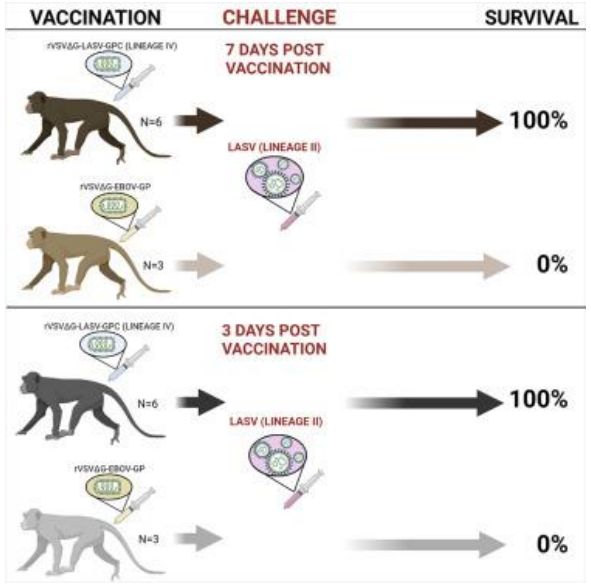


Figure 2. *A pool of high responding vaccinee samples was tested at 1:500 dilution for binding to LASV GP from Lineages II,III, IV and VII*



Cross R.Cell Reports 2022

CHALLENGES : MULTIPLES LINEAGES, DOSE REGIMEN

Table 4. Advanced LASV vaccine candidates tested in "proof-of-concept" efficacy trials in non-human primates (NHPs).

Vaccine Candidate	LASV Vaccine Antigen(s)	Vaccine Regimen	Efficacy against LASV		Viremia after Challenge [b]	Correlates of Protection	Ref
			Lineage IV [a]	Other Lineages			
Recombinant vaccinia virus	GP (JOS) NP GP&NP	Single vaccination, at four sites, total 1×10^9 PFU, ID	88% 20% 90%	ND	Low–moderate High Low–moderate	CMI	[47]
Reassortant MOPV/LASV, ML29	GP&NP (JOS)	One dose, 1×10^3 PFU, SC	100%	II–100% (*guinea pigs*)	<LD	Sterilizing CMI	[21,69,70,88]
rVSVΔG/LASVGPC	GP (JOS)	One dose, 1–6 × 10^7 PFU, IM	100%	I and V–100% (*guinea pigs*)	Low, transient	NAbs? CMI?	[23,46]
MV-LASV	GP & NP (JOS)	One dose, 2×10^6 $TCID_{50}$, SC	100%	ND	<LD	Non-NAbs and CMI	[51]
rVSV-N4ΔG-LASVGPC in Quadrivalent VesiculoVax	GP (JOS)	Two doses, 1×10^7 PFU, IM	-	II–100%	<LD in 4 of 5 NHPs.	ND	[86]
VEEV-TC83 RNA replicon particles	GP (JOS&LP)	Two doses, 1×10^7, SC	80%	20%	Moderate	ND	Lukashevich, Unpublished [27]
$MOPEVAC_{LASV}$	GP (JOS)	One dose, 6×10^6 PFU/dose, IM	100%	ND	Low, transient	Non-NAbs, CMI	[51]
DNA	GP (JOS)	Two immunizations, 20mg DNA at four sites, ID electroporation	100%	ND	ND	NAbs? CMI?	[78,79]

[a] Challenge dose: 1 × 103–1 × 104 PFU of LASV/JOS (Lineage IV), route of inoculation: SC or IM. LASV-Z32 (Lineage IV) was also used [23]. [b] Low–moderate, 103–104 PFU/mL; high, >104 PFU/mL. Abbreviations: JOS, LASV Josiah strain; LP, LASV LP strain (Lineage I); CMI, cell-mediated immunity; FFU, fluorescent forming units; GP, glycoprotein; GP and NP, simultaneous expression of NP and GP in the same vector; ID, intradermal; IM, intramuscular; LASV, Lassa virus; LD, limit of detection; NAbs, neutralizing antibody responses; ND, not done; NHP, non-human primate; NP, nucleoprotein; PFU, plaque-forming unit; SC, subcutaneous. Modified from: Lukashevich, I.S.; Paessler, S.; de la Torre, J.C. Lassa virus diversity and feasibility for universal prophylactic vaccine. F1000Research 2019, 8, F1000 Faculty Rev-134.

FUTURE DIRECTIONS AND PHASE 3 STUDY

Use the GPC in the prefusion state to overcome LASV diversity.

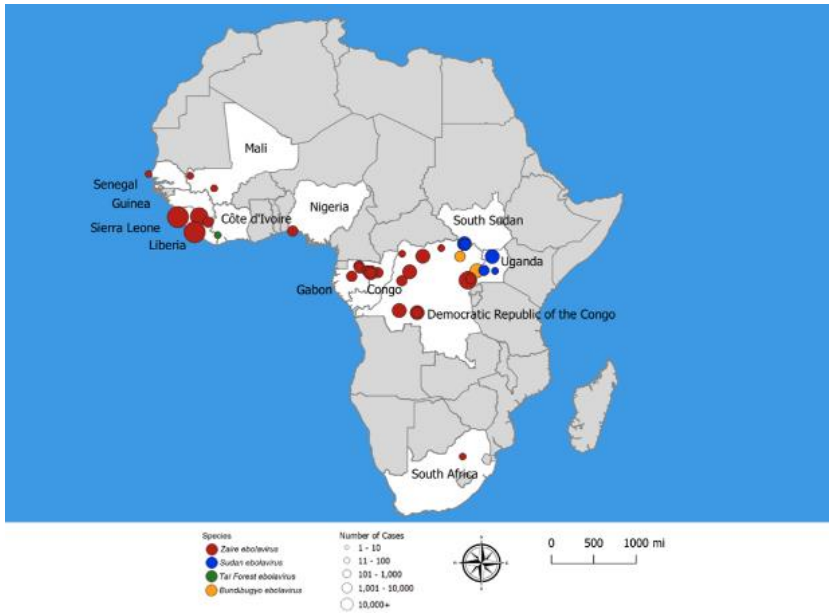
Phase 3 study

- Cellular immune response, incl T/B cell memory
- Long term protection against hospitalization
- Vaccine efficacy against LF associated death
- Vaccine efficacy against asymptomatic Lassa infections
- Review data for potential evidence for a CoP (would require post vaccination blood sample from every trial participants to analyse breakthrough cases)

EBOLA VIRUS DISEASE

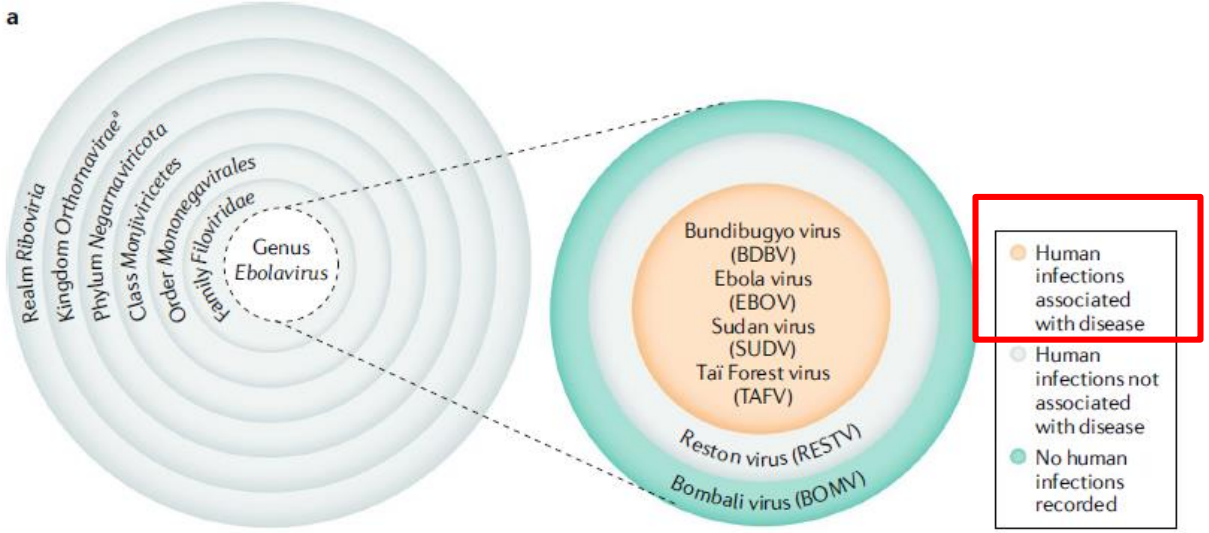
Epidemiology

- Discovered in 1976
- Epidemic (sporadic, small and large outbreak in multiple countries)



Virus

- Family: *Filoviridae*
- Genus: *Ebolavirus*
- Species : *Bundibugyo/Sudan/Zaire/Taï Forest/Reston/Bombali ebolavirus*



- Zoonosis → reservoir: bats??, vertebrates
- Transmission:
  - Animal (reservoir, vertebrates) to human, sporadic
  - Human to human +++

EBOLA VIRUS DISEASE

Disease

- Incubation 3-21 days
- Abrupt onset, aspecific acute febrile illness
- Narrow clinical sprectrum → severe illness

  -->Progression to shock and multiorgan failure
- CRF ~40-50% (25-90%), higher in pregnant women and in people less than 5 and over 40
- Long term impact:
  - Virus persistence (CNS, testes, eyes)
  - Arthralgias 87%
  - Ocular symptoms 14-60%
  - Social isolation, depression, cognitive deficit, long term disability

Public Health Impact

- Potential for large outbreak → most transmissible VHF
- Disease of caretakers
  - Healthcare workers
  - Funeral practices
  - Caretaking at home
- Increased in the frequency and size of outbreaks
- Neurological & psychological sequelae in survivors

EBOLA VIRUS DISEASE

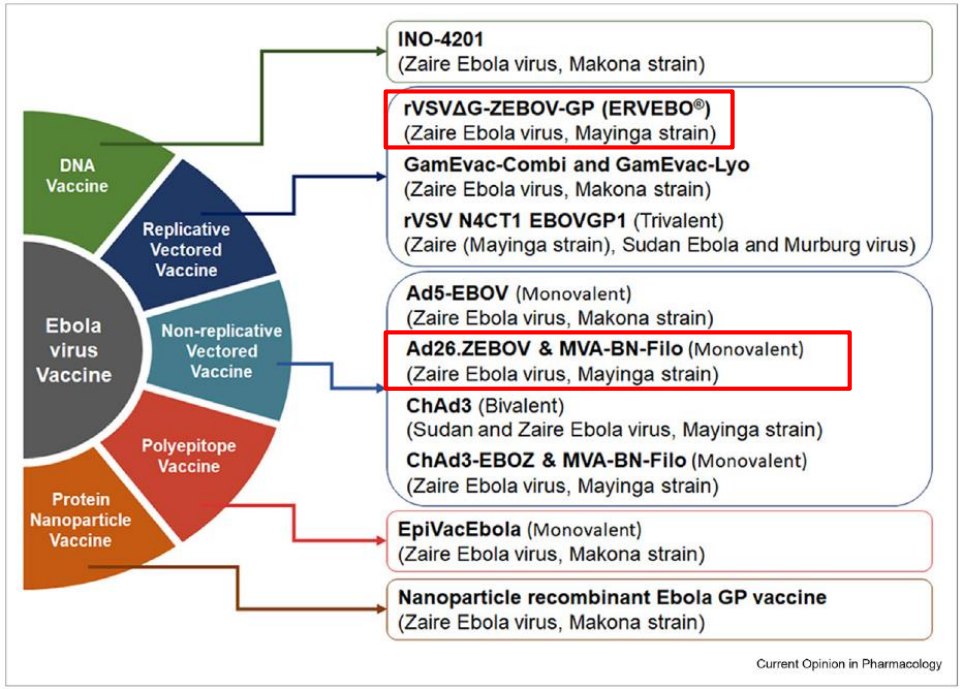
Outbreaks:

- 1976-1999: 10
- 2000-present: 23

Outbreaks Sudan virus disease: 8 (5 in Uganda)

Years	Country	Species	#Cases	#Deaths (CFR)
1976	Zaire (->DRC)	*Zaire ebolavirus*	318	280 (88%)
1976	Sudan (->South Sudan)	*Sudan ebolavirus*	284	151 (53%)
1977	Zaire (->DRC)	*Zaire ebolavirus*	1	1 (100%)
1979	Sudan (->South Sudan)	*Sudan ebolavirus*	34	22 (65%)
1994	Gabon	*Zaire ebolavirus*	52	31 (60%)
1994	Ivory Coast	*Thaï Forest ebolavirus*	1	-
1995	Zaire (->DRC)	*Zaire ebolavirus*	315	250 (81%)
1996	Gabon	*Zaire ebolavirus*	37	21 (57%)
1996	Gabon	*Zaire ebolavirus*	60	45 (74%)
1996	South Africa	*Zaire ebolavirus*	2	1 (50%)
2000	Uganda	*Sudan ebolavirus*	425	224 (53%)
2001	Gabon	*Zaire ebolavirus*	65	53 (82%)
2001	Republic of Congo	*Zaire ebolavirus*	57	43 (75%)
2002	Republic of Congo	*Zaire ebolavirus*	143	128 (89%)
2003	Republic of Congo	*Zaire ebolavirus*	35	29 (83%)
2004	Sudan (->South Sudan)	*Sudan ebolavirus*	17	7 (41%)
2007	DRC	*Zaire ebolavirus*	264	187 (71%)
2007	Uganda	*Bundibugyo ebolavirus*	149	37 (25%)
2008	DRC	*Zaire ebolavirus*	32	15 (47%)
2011	Uganda	*Sudan ebolavirus*	1	1 (100%)
2012	Uganda	*Sudan ebolavirus*	11	4 (36%)
2012	DRC	*Bundibugyo ebolavirus*	36	13 (36%)
2012	Uganda	*Sudan ebolavirus*	6	3 (50%)
2014-16	Multiple countries	*Zaire ebolavirus*	28646	11323 (39%)
2014	DRC	*Zaire ebolavirus*	66	49 (71%)
2017	DRC	*Zaire ebolavirus*	8	4 (50%)
2018	DRC	*Zaire ebolavirus*	54	33 (61%)
2018-20	DRC, Uganda	*Zaire ebolavirus*	3470	2287 (66%)
2020	DRC	*Zaire ebolavirus*	130	55 (42%)
2021	DRC	*Zaire ebolavirus*	12	6 (50%
2021	Guinea	*Zaire ebolavirus*	23	12 (52%)
2021	DRC	*Zaire ebolavirus*	11	6 (55%)
2022	DRC	*Zaire ebolavirus*	5	5 (100%)
2022	**Uganda**	***Sudan ebolavirus***	**ongoing**	**ongoing**

EBOLA VACCINE DEVELOPMENT



Current vaccine candidate of EBOV. EBOV, Ebola virus.

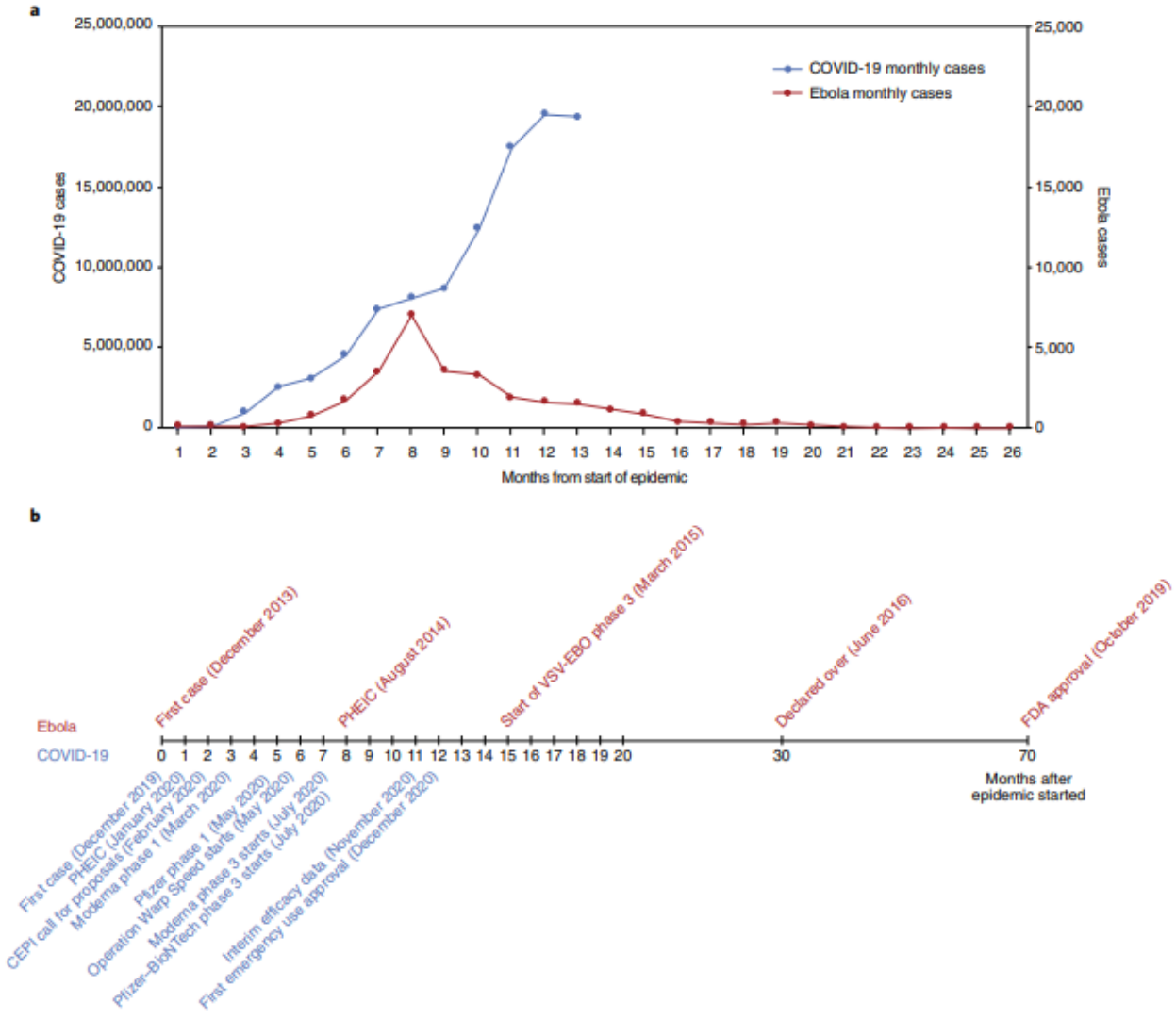


Fig. 1 | A comparison of the epidemic curves and vaccine development timelines between the 2014 West African Ebola outbreak and COVID-19. **a**, The number of months from the onset of the epidemic is shown against the number of reported cases per day. Note that the COVID-19 (left) and Ebola (right) axes are scaled differently. **b**, Vaccine development timelines for COVID-19 versus Ebola in the context of particular events during the respective outbreaks. PHEIC, public health emergency of international concern.

Excler Nature medicine 2021;

APPROVED EBOLA VIRUS DISEASE VACCINE

ERVEBO® (a.k.a. rVSV-ZEBOV-GP) (MERCK)

- Replication-competent, live, attenuated rVSV vectored vaccine
- Active against *Zaire ebolavirus*
- Single dose delivery, im (booster >6 months)
- Single-dose vials
- Logistics:
  - Storage at -80°C to -60°C protected from light
  - Storage refrigerated at 2°C to 8°C for 2 weeks possible
  - Thawing at room temperature. Usage within 4h.

- **FDA approved** for >18 (December 2019)
  - Vaccine eligibility (US 2020)
    - Ebola virus disease responders
    - Laboratorians and support staff working with live virus
    - Healthcare workers at federally designated Ebola Treatment Centers
- **European Medicines Agency approved** (2019)
- Approved in other countries
  - Burundi, Central African Republic, Democratic Republic of the Congo, Ghana, Guinea, Rwanda, Uganda, Zambia
- Insufficient data in pregnant women, children and immunocompromised persons
  - Use from 6m and older and pregnant women during outbreaks

Henao-Restrepo Lancet ID 2018; Huttner Lancet ID 2015; MMWR ACIP 202, Marzi Science 2015

APPROVED EBOLA VIRUS DISEASE VACCINE

- Complete protection after 7 days, partial protection after 3 days in NHPs
- Vaccine efficacy (100%) in human supported by a phase 3, open-label, cluster-randomized, controlled ring vaccination in Guinea (2014-16)
- In human: persistence of Ab response up to 2 years post vaccination
- No correlate of protection
- Booster?

1st generation of vaccine (reactogenecity)
Immunity against the VSV backbone? Long term immunity
Single dose delivery (outbreak)

- Adverse events (vaccine safety):
  - Reactogenecity +++
  - Arthralgia (onset 0-42 DPV) : 2.9 -40%
    - Reported within a few days, resolved within a week
    - Vaccine virus detected by rRT-PCR in 4 patients with joint complaints (no virus isolation)
    - Severe arthralgia (onset 0-42 DPV) : 0-1.7%, significant joint pain that prevents daily activities
  - Arthritis (onset 5-56 DPV) : 0-23.5%
    - Reported after 1 week (associated factors: sex-female and medical Hx of arthritis), resolved within weeks
  - Cutaneous vasculitis, vesicles
  - Serious adverse events: 3/15'399 (febrile Rx, anaphylactic Rx, influenza like illness)

Henao-Restrepo Lancet ID 2018; Huttner Lancet ID 2015; MMWR ACIP 202, Marzi Science 2015

APPROVED EBOLA VIRUS DISEASE VACCINE

Ad26.ZEBOV (Zabdeno®) and MVA-BN-Filo (Mvabea® (JANSSEN)

- Prime-boost delivery, im
- Dose primer Ad26.ZEBOV
  - Non replicating, recombinant viral vector
  - Human Adenovirus encoding the *zaire ebolavirus GP*
- Booster with MVA-BN-Filo (8wks later)
  - Non replicating, viral vector
  - MVA encoding the GP *zaire* and *sudan ebolavirus*, Marburg virus and the NP *Tai Forest ebolavirus*

- Logistics
  - Storage at -85 to – 55°C
  - Transportation frozen at -25°C to -15°C
  - Storage at 2-8°C for up to 8 month for Ad26.ZEBOV and up to 1 month for MVA-BN-Filo
- Approved by EMA 2020
- Clinical studies: Phase 1,2, 3 (Europe, US, Africa) → data on safety & immunogenicity, no study on the efficacy of preventing ebola virus disease in an outbreak situation.
  - Healthy adults, HIV+, Children
- Special populations :
  - Insufficient data in pregnant and breastfeeding women, and immunocompromised
  - Authorized by the EMA for children aged > 1 year
- Safety profile acceptable (fewer AEs than rVSV platform)
- Persistance AB at 1 year 50-100%

Limited impact of vector immunity
Ability to accommodate multigene inserts
Vector stability
Better tolerated
Not suitable for outbreaks?

Winslow JAMA 2017; Milligan ID JAMA 2016; Ishola Lancet ID 2022; WHO GACVS meeting 2019; EMA

EBOLA VIRUS VACCINE CANDIDATES

Table 2

Clinical trials of Ebola virus vaccines.

Approved vaccine for EBOV

Name	Species	Developer	License	Phase	Year	Ref
ERVEBO® (rVSV-ZEBOV-GP, v920)	Zaire EBOV	Merck Sharp and Dohme Corp.	U.S. License No. 0002	FDA approved	2019	[25,31]
GamEvac-Combi (vaccine)	Zaire EBOV	Russian Federation	Licensed in Russia	–	2019	[34]
Zabdeno and Mvabea (Ad26.ZEBOV, MVABN-Filo)	Zaire EBOV	Johnson &Johnson	–	Approved in EU	2020	[34,37]
Ad5-EBOV	Zaire EBOV (Makona)	Academy of Military Medical Sciences and CanSino Biologics	Licensed in China	-	2017	[34,43,44]

Clinical trial status of vaccines for EBOV (Clinical Trials (www.clinicaltrials.gov), **FDA** (www.fda.gov)) [40,42]

Name	Species	Country	Phase	Status	Period	Ref
Ad26.ZEBOV Batch #1, 2 and 3, MVA-BN-Filo	Zaire EBOV	USA	Phase 3	Completed	2015–2016	[40]
(ChAd3-EBO-Z) (GSK3390107A)	Zaire EBOV (Mayinga)	Cameroon, Mali, Nigeria, Senegal	Phase 2	Completed	2015–2016	[45,46]
VSV-GZEBOV, ChAd3-EBO Z	Zaire EBOV	Liberia	Phase 2	Active, not recruiting	2015–2020	[47]
Ad26.ZEBOV, MVABN-Filo, rVSV#GZEBOV-GP	Zaire EBOV	Guinea, Liberia, Mali, Sierra Leone	Phase 2	Active, not recruiting	2017–2024	[40]
cAd3-EBOZ vaccine	Zaire EBOV (Mayinga)	Switzerland	Phase 1, Phase 2	Completed	2014–2015	[32]
GamEvac-Lyo, GamEvac-Lyo (component A), GamEvac-Lyo (component B)	Zaire EBOV	Russian Federation	Phase 1, Phase 2	Completed	2017–2018	[40]
BPSC-1001 (VSV#G-ZEBOV)	Zaire EBOV	Unknown	Phase 1	Completed	2014–2015	[40]
(cAd3-EBO Z), Booster-MVA-BN® Filo	Zaire EBOV (Mayinga)	Mali	Phase 1	Completed	2014–2016	[32,47]
HPIV3-EbovZ GP Vaccine	Zaire EBOV	USA	Phase 1	Completed	2015–2016	[40]
VRCEBOADC069-00-vp, MVA-EbolaZ	Zaire EBOV	Mali	Phase 1	Completed	2015–2016	[40]
cAd3-EBO Z, MVA-BN® Filo	Zaire EBOV (Mayinga)	UK	Phase 1	Completed	2014–2017	[32,47]
INO-4201, INO-9012	Zaire EBOV	USA	Phase 1	Completed	2015–2018	[40]
HPIV3/#HNF/EbovZ GP vaccine	Zaire EBOV	USA	Phase 1	Active, not recruiting	2018–2020	[40]
ChAd3-EBO-Z, MVA Multi-Filo Ebola Vaccine	Mayinga EBOV	USA	Phase 1	Completed	2018–2020	[32,47]
cAd3- EBO S vaccine	Zaire EBOV (Mayinga)	Uganda	Phase 1	Completed	2019–2020	[47]
cAd3-Marburg cAd3-EBO-S	Zaire EBOV (Mayinga)	USA	Phase 1	Recruiting	2021	[47]

Sharma Science Direct 2021

VACCINE CURRENTLY IN FIELD TRIAL: SUDAN VIRUS DISEASE

WHO R&D Blueprint meeting

- **cAd3**
- **chAdOX1**
- **rVSV SUDV GP**

- **cAd3-EBO S (NIAID/Sabine institute)**
  - Chimpanzee adenovirus serotype 3 vectored Ebola vaccine encoding the *sudan ebolavirus* GP
  - Phase I studies (safety, tolerabilit and Immunogenecity) completed in Uganda and US: results not published yet

RCT protocol development

- cRCT ring vaccination of contact (randomized to vaccination now and in 21 days)

MARBURG VIRUS DISEASE

Epidemiology

- Discovered in 1967
- Epidemic (sporadic and large outbreak in multiple countries)

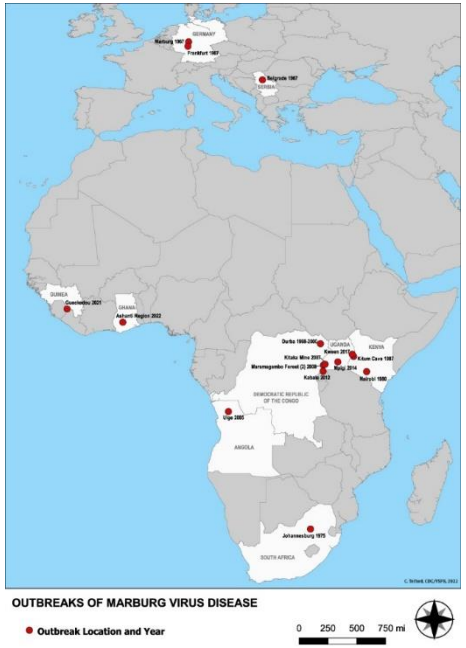
Virus

- Family: *Filoviridae,* Genus: Marburg virus, Species: *Marburg marburgvirus*
- Zoonosis → reservoir: bats → vertebrates
- Transmission:
  - Animal (reservoir, vertebrates) to human (exposition to bat faeces)
  - Human to human +++

Disease

- Incubation 2-21 days
- Aspecific acute febrile illness (abrupt onset)
- Narrow clinical sprectrum → severe illness
- CRF 70-85%

Public Health impact (travelers?)



Years	Origin (country)	#cases	#deaths (CFR)
1967	Uganda (Germany)*	31	7 (23%)
1975	Zimbabwe (South Africa)	3	1 (33%)
1980	Kenya (Kenya)	2	1 (50%)
1987	Kenya (Kenya)	1	1 (100%)
1990	Russia (Russia)*	1	1 (100%)
1998-2000	Durba (DRC)	154	128 (83%)
2004-2005	Uige Province (Angola)	252	227 (90%)
2007	Glod mine Kamwenge (Uganda)	4	1 (25%)
2008	Cave Maramagambo (Uganda)	1	-
2008	Cave Maramagambo (Uganda)	1	1 (100%)
2012	Kabale (Uganda)	15	4 (27%)
2014	Kampala (Uganda)	1	1 (100%)
2017	Kween (Uganda)	4	3 (75%)
2021	Guéckédou (Guinea)	1	1 (100%)
2022	Ashanti region (Ghana)	ongoing	ongoing

- Angola
- DR Congo
- Germany
- Ghana
- Guinea
- Kenya
- Serbia
- South Africa
- Uganda

Outbreaks:

1967-2022 (33 ans): 7

2022-2022 (22 ans): 8

MARBURG VIRUS DISEASE VACCINE CANDIDATE

- **DNA vaccine (NIH)**
  - DNA vaccine expressing the GP from the Marburg virus
  - Phase I studies: Vaccine immunogenecity and safety
    - Well tolerated, no serious adverse events

rVSV N4CT1 (ProfectusBioSciences Inc)

- Replication-competent, live, attenuated rVSV vectored vaccine encoding the Marburg virus GP
- Preclinical studies: Vaccine effiacy in NHPs

Table 2. Protective efficacy studies of MARV vaccines in NHPs.

Vaccine Modality	Challenge Virus	Vaccine Doses	Time to Challenge (d)	Survival (%)	Ref. #
Inactivated Virus					
Inactivated MARV	MARV	2	21	50	44
Replication Incompetent Vaccines					
Virus-like Replicon Particle (VRP)					
VRP-MARV GP	MARV	3	35	100	45
VRP-MARV NP	MARV	3	35	67	45
VRP-MARV GP + VRP-MARV NP	MARV	3	35	100	45
Adenovirus Vector					
Ad5.MARV GP	MARV	1	28	100	46
CAdVax-panFilo	MARV	2	42	100	27
DNA					
MARV GP	MARV	4	21	100	46
MARV GP	MARV	3	28	67	47
MARV GP	MARV	3	56	83	30
EBOV GP + SUDV GP + MARV GP + RAVV GP	MARV	3	56	100	30
VLP					
MARV GP, MARV GP + NP	MARV	3	28	100	48
MARV GP/NP/VP40 + Poly-IC	MARV	3	28	100	49
MARV GP/NP/VP40 + QS-21	MARV	3	28	100	49
Replication Competent Vaccines					
Recombinant Vesicular Stomatitis Virus					
VSV-MARV	MARV	1	28	100	39
VSV-EBOV + VSV-SUDV + VSV-MARV	MARV	1	28	75	40
Mixed Modality					
MARV GP DNA + Ad5.MARV GP	MARV	4	42	100	46

Suschack Human vaccines&Immunotherapeutics 2019; Woolsey Plos NTD 2022

COMBINED FILOVIRUS VACCINE CANDIDATES

ChAd3-EBOV (GSK)

- Non replicating, simian adenovirus (serotype 3) vectored vaccine encoding for the *zaire ebolavirus* GP
- Administration as a single intramuscular dose
- Also combined with the *sudan ebolavirus* GP (primer)
- Also studied in combination with an MVA-BN-Filo (booster)
- Phase I studies (safety and immunogenecity)
- Phase II studies in Cameroon, Mali, Nigeria and Senegal
  - Adults and children
  - No AEs
  - 92% Ab at 1 month, 88-90% persitence Ab at 1 year

DNA vaccine (NIH)

- DNA vaccine expressing the GP from the *zaire and sudan ebolavirus*
- Phase I studies: Vaccine immunogenecity and safety
  - Well tolerated, no serious adverse events

Ad26.Filo & MVA-BN-Filo (JANSSEN)

- Replicant-incompetent human Adenovirus 26 vectored vaccine encoding the GP of the *zaire and sudan ebolavirus*, and Marburg virus
- Non replicating, MVA viral vector encoding the GP of *zaire* and *sudan ebolavirus*, Marburg virus and the NP of *Tai Forest ebolavirus*
- Preclinical studies: Vaccine efficacy in NHPs, persistance Ab >1 year
- Phase I study: Vaccine immunogenecity and safety

ChAdOx1 biEBOV (University of Oxford)

- Bivalent chimpanzee engineered adenovirus serotype Y25 vectored vaccine encoding the *zaire and sudan ebolavirus* GP
- Phase I studies I (UK), Ib (Tanzania): result not published yet

De santis Lancet ID 2016; Ewer NEJM 2016; Tapia Lancet ID 2016; Suschack Hum Vac&IT 2019; Bockstal Plos One 2022; Sarwar JID 2015

https://www.who.int/publications/m/item/sudan-virus-vaccine-tracker---list-of-vaccine-candidates-in-research---development;

COMBINED FILOVIRUS VACCINE CANDIDATES

Table 4. (Continued).

NCT Number	Viral Target	Vaccine	Phase	Study Dates	Country
NCT02509494	EBOV SUDV TAFV MARV	ChAd3.EBOV+MVA-BN-Filo	3	Study Start: Sept. 2015 Study Completion: Aug. 2019	Sierra Leone
NCT02911415	EBOV	VSV-EBOV+Ad5.EBOV	1	Study Start: Sept. 2016 Study Completion: Dec. 2017	Russian Fed.
NCT03072030	EBOV	VSV-EBOV+Ad5.EBOV Placebo	4	Study Start: Aug. 2017 Study Completion: Dec. 2019	Guinea Russian Fed.
NCT02344407	EBOV	VSV-EBOV ChAd3.EBOV Placebo	2	Study Start: Jan. 2015 Study Completion: June 2020	Liberia
NCT03140774	EBOV SUDV TAFV MARV	Ad26.EBOV+MAV-BN-Filo VSV-EBOV		Study Start: May 2017 Study Completion: July 2020	UK
NCT03583606	EBOV SUDV TAFV MARV	ChAd3.EBOV+MVA-BN-Filo	1	Study Start: Oct. 2018 Study Completion: Aug. 2020	USA
NCT02661464	EBOV SUDV TAFV MARV	Ad26.ZEBOV MVA-BN-Filo	3	Study Start: May 2016 Study Completion: April 2023	USA Burkina Faso Côte D'Ivoire France
NCT02661464	EBOV SUDV TAFV MARV	Ad26.ZEBOV MVA-BN-Filo	3	Study Start: May 2016 Study Completion: April 2023	USA Burkina Faso Côte D'Ivoire France

Suschack Hum Vac&IT 2019

Table 4. Clinical trials with patients receiving combined filovirus vaccine candidates.

NCT Number	Viral Target	Vaccine	Phase	Study Dates	Country
NCT03140774	EBOV SUDV TAFV MARV	Ad26.EBOV+MAV-BN-Filo VSV-EBOV	1/2	Study Start: May 2017 Study Completion: July 2020	UK
NCT02313077	EBOV SUDV TAFV MARV	MVA-BN-Filo Ad26.EBOV Placebo	1	Study Start: Dec. 2014 Study Completion: March 2016	UK
NCT02267109	EBOV SUDV TAFV MARV	ChAd3.EBOV+MVA-BN-Filo ChAd3.EBOV+Placebo	1	Study Start: Oct. 2014 Study Completion: April 2016	Mali
NCT02376426	EBOV SUDV TAFV MARV	Ad26.EBOV MVA-BN-Filo	1	Study Start: March 2015 Study Completion: June 2016	Kenya
NCT02543268	EBOV SUDV TAFV MARV	Ad26.EBOV MVA-BN-Filo	3	Study Start: Sept. 2015 Study Completion: July 2016	USA
NCT02368119	EBOV SUDV TAFV MARV	ChAd3.EBOV+MVA-BN-Filo	1	Study Start: March 2015 Study Completion: Sept. 2016	Mali
NCT02376400	EBOV SUDV TAFV MARV	MVA-BN-Filo Ad26.EBOV Placebo	1	Study Start: April 2015 Study Completion: Sept. 2016	Tanzania Uganda
NCT02543567	EBOV SUDV TAFV MARV	Ad26.EBOV MVA-BN-Filo	3	Study Start: Sept. 2015 Study Completion: Nov. 2016	USA
NCT02408913	EBOV SUDV TAFV MARV	MVA-BN-Filo ChAd3.EBOV+MVA-BN-Filo	1	Study Start: March 2015 Study Completion: April 2017	USA
NCT02325050	EBOV SUDV TAFV MARV	MVA-BN-Filo Ad26.EBOV Placebo	1	Study Start: Jan. 2015 Study Completion: May 2017	USA
NCT02451891	EBOV	MVA-EBOV ChAd3.EBOV	1	Study Start: April 2015 Study Completion: Aug. 2017	UK
NCT02240875	EBOV SUDV TAFV MARV	ChAd3.EBOV+MVA-BN-Filo	1	Study Start: Sept. 2014 Study Completion: Aug. 2017	UK
NCT02495246	EBOV	ChAd3.EBOV Ad26.EBOV	1	Study Start: Sept. 21, 2015 Study Completion: Aug. 2017	UK
NCT02416453	EBOV SUDV TAFV MARV	MVA-BN-Filo Ad26.EBOV Placebo	2	Study Start: June 2015 Study Completion: Jan. 2018	France UK
NCT02598388	EBOV SUDV TAFV MARV	Ad26.EBOV MVA-BN-Filo	2	Study Start: Jan. 2016 Study Completion: Dec. 2018	USA Kenya Mozambique Nigeria Tanzania Uganda
NCT02354404	EBOV SUDV	ChAd3.EBOV ChAd3.EBOV+ChAd3.SUDV MVA-EBOV	1	Study Start: Jan. 2015 Study Completion: April 2017	Uganda
NCT02891980	EBOV SUDV TAFV MARV	Ad26.EBOV MVA-BN-Filo	1	Study Start: March 2017 Study Completion: March 2019	USA
NCT02876328	EBOV SUDV TAFV MARV	Ad26.EBOV MVA-BN-Filo VSV-EBOV Placebo	2	Study Start: March 2017 Study Completion: March 2019	Guinea Liberia Mali Sierra Leone
NCT02564523	EBOV SUDV TAFV MARV	Ad26.EBOV+MVA-BN-Filo Placebo	2	Study Start: Nov. 2015 Study Completion: March 2019	Burkina Faso Côte D'Ivoire Kenya Uganda

(Continued)

CONCLUSION

2014-16 Ebola outbreak changed the paradigm

- 2 approved vaccines for Ebola virus disease (*zaire ebolavirus*)
  - rVSV:
    - Long term immunity
    - Immunogenecity in HIV+
    - Suitable for large scale vaccination campaign
  - Ad26-MVA
    - Logisitics (2 dose regimen)
- Significant number of phase I/II data from different vaccine platforms and in different populations for EBOV, SUDV, MARV, LASV
- Experience in conducting trials in emerging settings

- Need for more potent and versatile vaccine platforms
- Role of combined filovirus (+/-LASV) vaccines ?
- More understanding on the disease pathogenesis is required