Statistical considerations: Trial design and sample size

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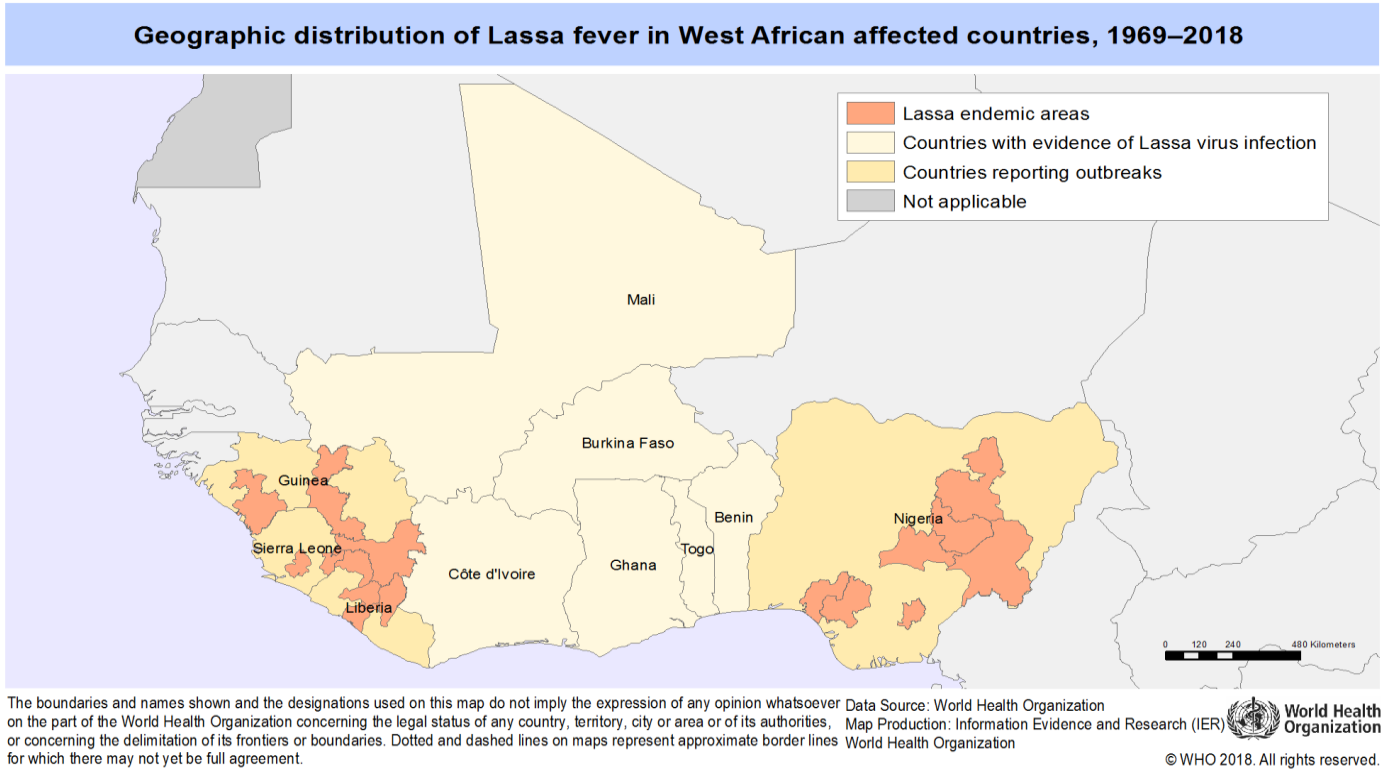
Powering research to prevent epidemics

Will there be sufficient sample size?

Lassa fever is endemic in Benin, Ghana, Guinea, Liberia, Mali, Sierra Leone, and Nigeria, but probably exists in other West African countries as well.



Lassa in Nigeria

Seasonal transmission in Nigeria: large outbreaks in Jan/Feb

- 2022: 937 confirmed and 6,883 suspected cases, 173 confirmed deaths
- 2021: 482 confirmed and 4,654 suspected cases, 102 confirmed deaths
- 2020: 1181 confirmed and 6,732 suspected cases, 244 confirmed deaths
- 2019: 833 confirmed and 5,057 suspected cases, 174 confirmed deaths

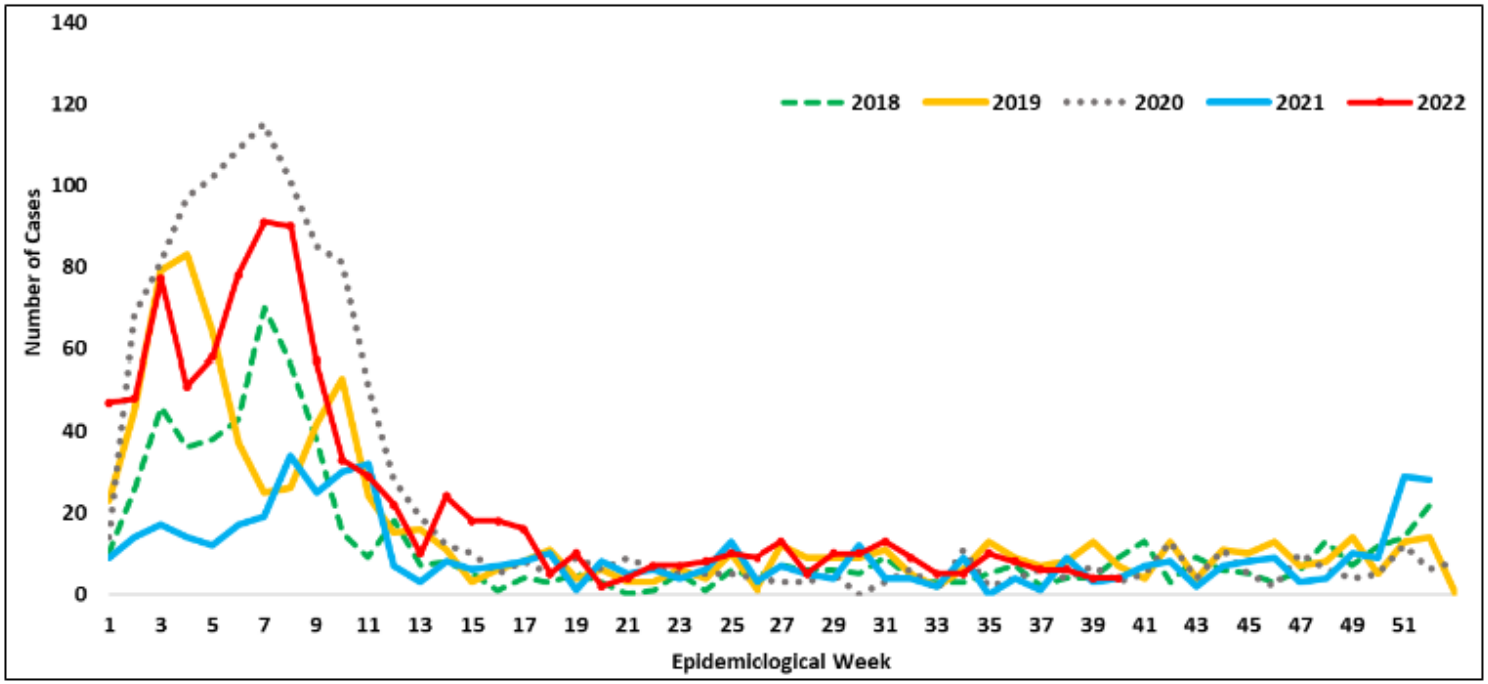
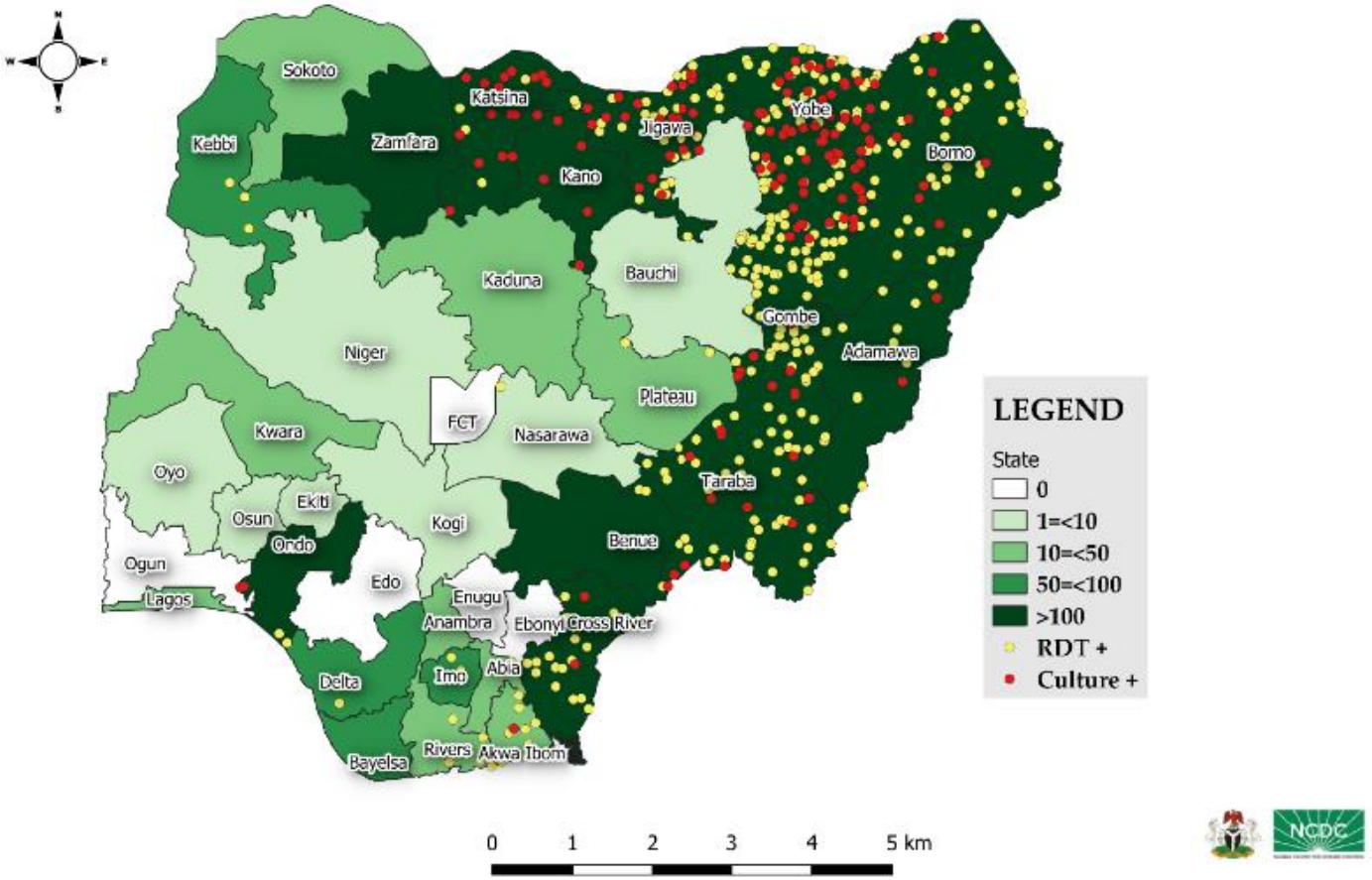


Figure 6: Trend of confirmed cases by epidemiological week, 2018– 2022, Nigeria

https://www.ncdc.gov.ng/diseases/info/L

Lassa in Nigeria



Map of Nigeria showing states with RDT + Culture and suspected cases, week 1 - 39, 2022

https://www.ncdc.gov.ng/themes/common/files/sitreps/983477614bd2dc4fe1250b98efc113d8.pdf

Lassa – target product profile scenarios

Emergency setting (Reactive/Outbreak use):

Protection of **at-risk persons in the area of an ongoing outbreak of Lassa fever.**

Non-emergency setting (Preventive Use):

Populations living in **areas where Lassa fever is endemic**, particularly HCW in endemic areas.

Vaccine trial structure and conduct

- Core, platform randomized trial
  - Dean NE, et al. Creating a framework for conducting randomized clinical trials during disease outbreaks. *New England Journal of Medicine* **382,** 1366-1369 (2020).
- Combining information across randomization structures for vaccine trials
  - Longini IM, et al. A platform trial design for preventive vaccines against Marburg virus and other emerging infectious disease threats. *Clinical Trials* (2022) https://doi.org/10.1177/17407745221110880.

Lassa – vaccine trial design

A prospective, randomized, double-blind, placebo-controlled, efficacy trial

Individual randomization in geographic clusters in areas mapped to have transmission, mixture of

- Pre-selected, pre-vaccinated clusters of highest risk
- Closely monitored high-risk clusters with responsive vax
- Responsive addition of clusters with transmission

Lassa – endpoint considerations

Primary endpoint

Laboratory-confirmed Lassa clinical illness

Secondary endpoints

- Infection (could move to co-primary endpoint)
- Stratified analyses on prior immune measures
- Stratified analyses on different lineages and/or clades (sieve analysis)
- Death
- Immunological correlates of risk and surrogates of protection, i.e., surrogates for vaccine efficacy

Statistical analysis

The primary analysis will be the estimated vaccine efficacy against confirmed Lassa illness: $\widehat{\mathrm{VE}} = 1 - \widehat{\lambda_1}/\widehat{\lambda_0}$

- $\widehat{\lambda_1} =$ estimated hazard of illness for individuals who receive vaccine.
- $\widehat{\lambda_0} =$ estimated hazard of illness for individuals who receive placebo.

One-sided hypothesis test for the primary outcome:

- H_0: $\mathrm{VE} \leq 0.3$ versus H_a: $\mathrm{VE} > 0.3$. In addition, a lower 95% confidence bound will be calculated for $\widehat{VE}$

Secondary analyses using same setup

Statistical method: Cluster-stratified, Cox proportional hazards model, with appropriate α – spending for interim analyses

The case of Lassa vaccine trials

Emergency setting (Reactive/Outbreak Use)

- It may be possible to accumulate enough data to assess VE in a single season

Non-emergency setting (Preventive Use)

- It will probably involve several years and a variety of locations to accumulate enough cases to assess VE
- We could combine data from the preventive and reactive trials to get an answer sooner

Individual randomization within sites

Multiple sites/outbreaks

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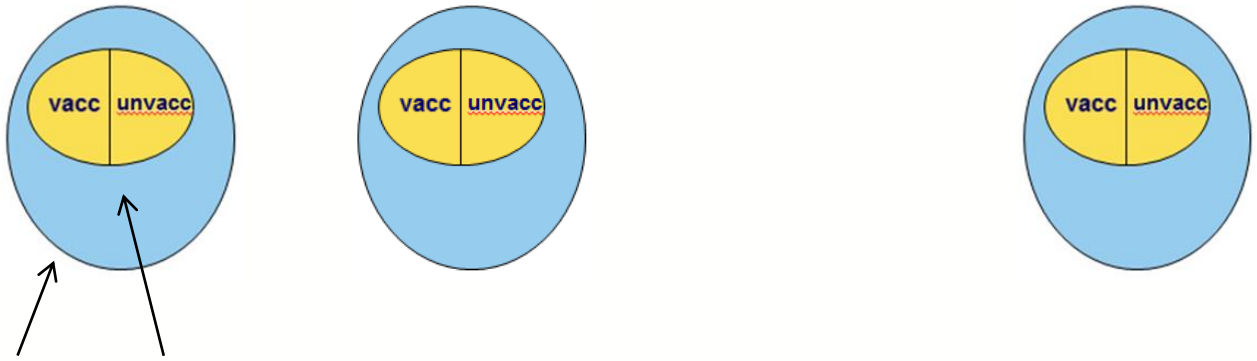


Sites Enrolled participants within sites

VE = 1 - $\frac{\lambda_1}{\lambda_0}$, combined across the n sites as stratification or regression

Sample Size for Primary Outcome With One Vaccine

90% power, 2:1 vaccine to placebo, α = 0.05 one-sided, VE = 0.3 lower bound, 20% loss-to-follow-up

VE	Average required total # of events	Cumulative attack rate in placebo arm	Cumulative attack rate in vaccination arm	Sample size in placebo arm	Sample size in vaccination arm	Total sample size
50%	360	0.5%	0.25%	44292	88583	132875
		1%	0.50%	22292	44583	66875
		1.5%	0.75%	15208	30417	45625
		2%	1.01%	11292	22583	33875
70%	62	0.5%	0.15%	9667	19333	29000
		1%	0.30%	4875	9750	14625
		1.5%	0.45%	3250	6500	9750
		2%	0.60%	2458	4917	7375
90%	19	0.5%	0.05%	3792	7583	11375
		1%	0.10%	1917	3833	5750
		1.5%	0.15%	1292	2583	3875
		2%	0.20%	1000	2000	3000

Sample size summary

- To reject vaccines with VE ≤ 30% and find those with VE > 50%
  - **62** cases across these two arms (vaccine and comparator), maximum of about **15,000** total participants.
  - Two interim analyses at **21** and **41** cases using Obrien-Fleming boundaries for early termination
- In Nigeria alone for 2019-2022, there were an average of about **850** confirmed cases per year, so we should have sufficient sample size with the proposed design

Interim monitoring boundaries defining benefit and lack-of-benefit

Information Fraction (Number of Events)	Nominal one-sided significance level	Approximate HR at benefit boundary*	Approximate HR at lack-of-benefit boundary*
1/3 (21 events)	0.0003	≤ 0.26 (VE > 0.74)	≥ 1.07 (VE < -0.07)
2/3 (41events)	0.0071	≤ 0.43 (VE > 0.57)	≥ 0.65 (VE < 0.35)
3/3 (62 events)	0.0225	≤ 0.50 (VE > 0.50)	≥ 0.55 (VE < 0.45)

“Core protocol” approach

The protocol should be generalizable to other West African countries where Lassa is endemic

Where outbreaks in other countries occur, the trial structure should allow new sites in affected areas to be added

Researchers and national representatives from affected countries should be engaged early on

A clear and transparent mechanism for achieving consensus regarding elements of the protocol is required (e.g. managing data, sharing samples, mediating disagreements)

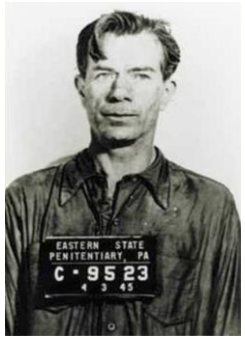
Trial governance

- Trial oversight will be provided by a **single Steering Committee** (SC) and a **single data monitoring committee** (DMC).
- Adaptive aspects of the study, to the extent not predefined in the protocol, will be governed by the SC, which will not have access to unblinded study data.
- The role of the DMC will be to apply pre- (and SC-) defined benefit and lack of benefit criteria to the vaccines, and to address potential safety issues as well as data integrity issues.
- Once one or more vaccines meet specified success criteria, new efficacy/lack of benefit criteria will be introduced.

Thank you

Reactive vaccination
Willie Sutton approach ……

- American bank robber in the 1930's, Willie Sutton



- When caught, he was asked "Willie why do you rob banks?"
- His answer, "Because that's where the money is."
- … so we want to put the vaccine and comparator where the cases will be

Human to human transmission

- Some human-human transmission due to close contact in settings like hospitals and households
  - Direct contact with the blood, urine, faeces, or other bodily secretion
- Epidemiological risk factors are obvious ones for rodent infestations, contact with wild rodents, or close contact with human cases.
- Hospital staff are at risk for infection unless protective measures and proper sterilization methods are used.

Lassa fever – basic facts

Incubation period: from 6–21 days

Serial interval: around 12 days or so

Pathogenicity: 20%

- 80% infections are asymptomatic

Numerous infections are mild or even asymptomatic

R_0 < 1 among humans, 5-7% household SAR, maybe up to 10% in HCWs with nosocomial exposure

In countries and regions with transmission, infection is fairly common, with seroprevalence up to 60%. More serosurveys are needed.