

An R&D Blueprint for action to prevent epidemics

Phase IIb and III

Lassa Fever Vaccine Trials Design

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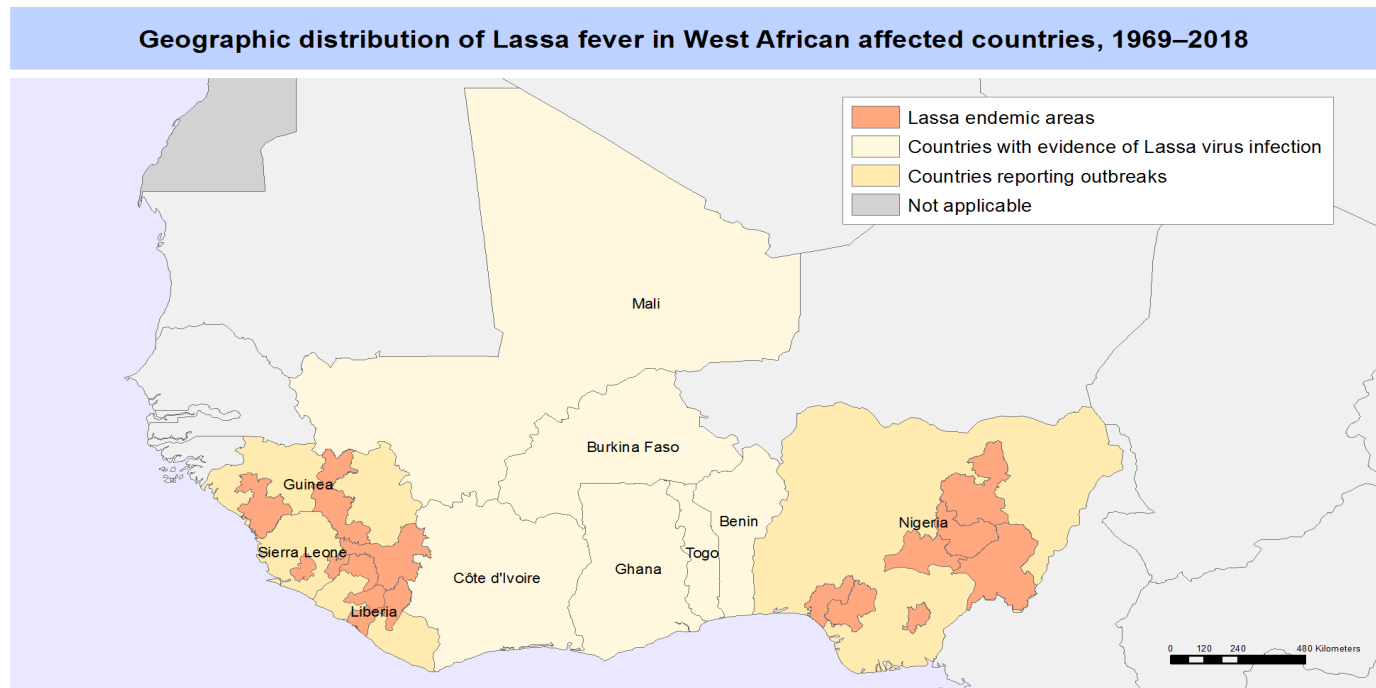
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Lassa fever – basic facts

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



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Data Source: World Health Organization
Map Production: Information Evidence and Research (IER) World Health Organization

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Lassa fever – basic facts

Overall case-fatality rate is 1%.

Observed case-fatality rate among patients hospitalized with severe cases of Lassa fever is 15% or 20-25%

Primary transmission from rodents to humans

Some human-human transmission due to close contact in settings like hospitals and households.

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%

Numerous infections are mild or even asymptomatic

$R_0 < 1$ among humans, 5-7% SAR, maybe up to 10% in HCWs

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

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.

Lassa – target vaccine population

Options:

Healthy adults and children, excluding pregnant and lactating women, immunodeficient people, small children

(or include some of the above depending on the vaccine and other factors)

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

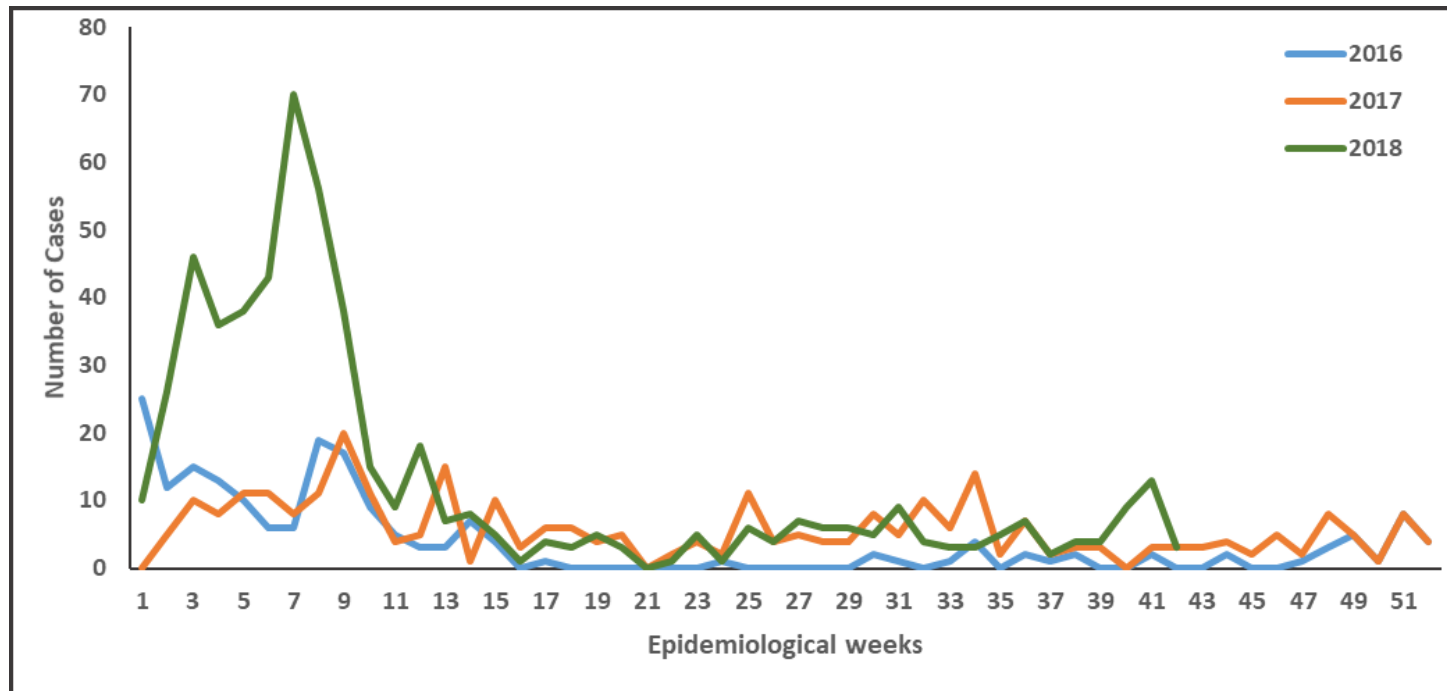
- Pre-selected, pre-vaccinated clusters of highest risk
- Closely monitored high-risk clusters with responsive vax
- Responsive addition of clusters with transmission

Also include health-care workers

Lassa in Nigeria

Seasonal transmission in Nigeria with a large outbreak in Jan/Feb 2018

- 2016: 109 confirmed cases
- 2017: 143 confirmed cases
- 2018 (as of 28 October): 548 confirmed and >2800 suspected



<https://www.ncdc.gov.ng/diseases/sitreps/>

Lassa in Nigeria

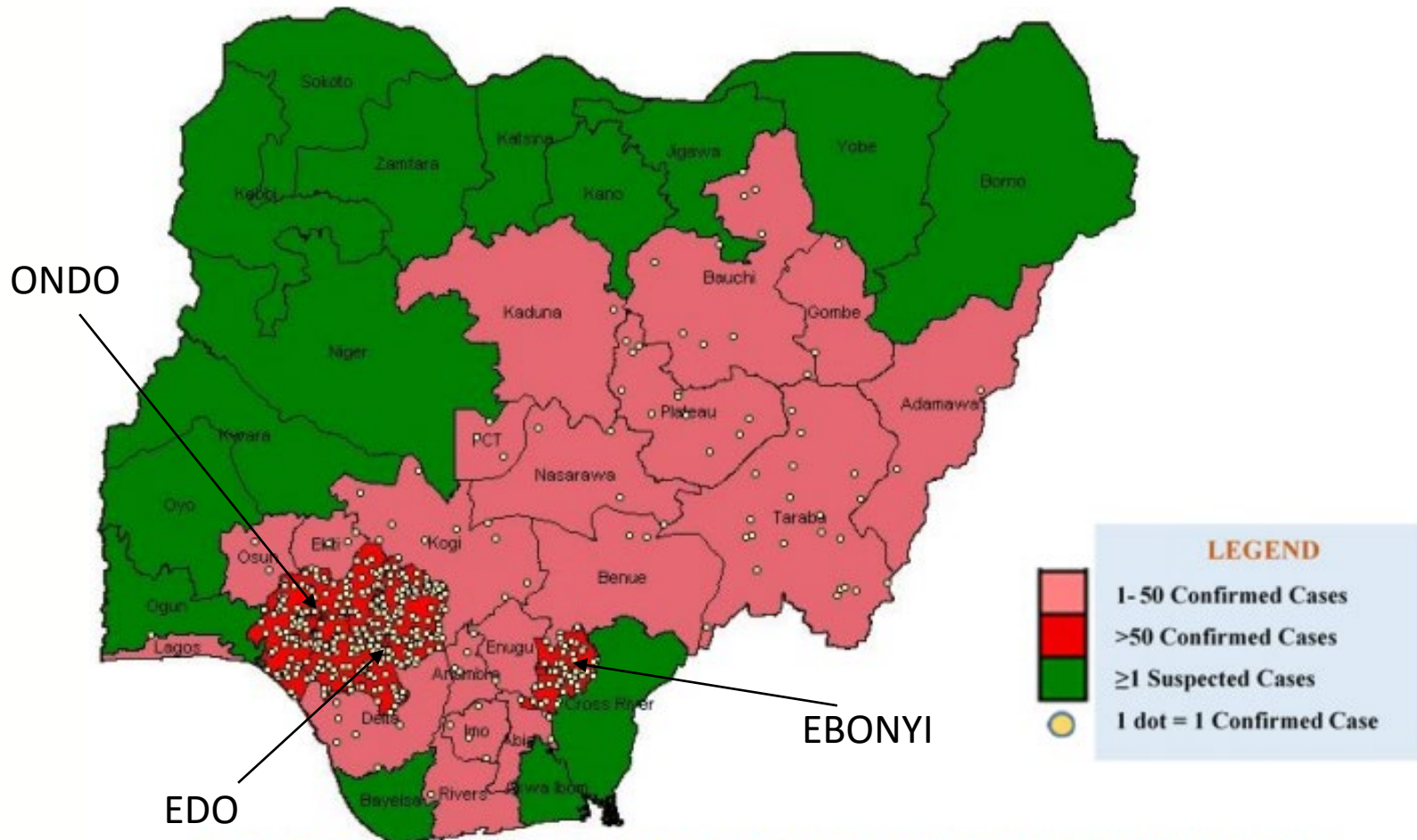


Figure1. Distribution of Confirmed Lassa Fever cases in Nigeria as at 28th October, 2018

<https://www.ncdc.gov.ng/diseases/sitreps/>

Lassa – important considerations

Screening at baseline

Bleed all of the trial participants before vaccination to determine baseline seropositivity

Could contribute to design an immune correlate of protection, with this design, if the vaccine works.

Lassa – endpoint considerations

Primary endpoint

Laboratory-confirmed Lassa clinical illness

Secondary endpoints

- Infection (could move to 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: $\widehat{VE} = 1 - \widehat{\lambda}_1/\widehat{\lambda}_0$

- $\widehat{\lambda}_1$ = 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:

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

Secondary analyses using same setup

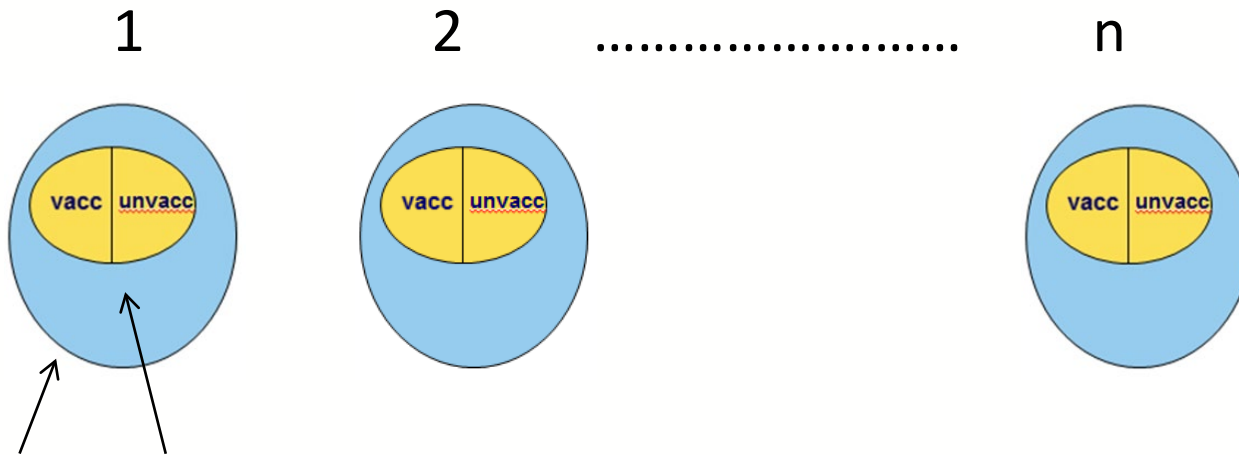
Statistical method: Cluster-stratified, Cox proportional hazards model, with appropriate α – spending for interim analyses

Testing more than one vaccine

- We can test m vaccines against a single placebo arm, using Bonferroni or a more complex correction for α
- e.g., two vaccines would be randomized in a 1,1,1 pattern with two hypothesis tests, each at $\alpha = 0.025$

Individual randomization within sites

Multiple sites/outbreaks



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, $\alpha = 0.05$ 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

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, but two seasons will probably be needed

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

Data monitoring strategy

Interim analyses to assess efficacy or futility can be timed to occur at the end of each season (or after reaching a targeted # of events, e.g. 50%)

Study data would not be released unless the trial was stopped, for efficacy, futility, or reaching its targeted number of endpoints

“Master 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)

Mathematical models for Lassa transmission in Nigeria other countries at risk of Lassa is under development

- Help design vaccine trial, including more accurate power calculations
- Use to determine vaccination strategies and their impact once we have an efficacious vaccine

Data needed for Lassa vaccine trial

1. Illness incidence data for confirmed cases
 - a) Data for each area/site
 - b) Secondary attack rate data for smaller groups such as hospitals, clinics and households
2. Infection prevalence and incidence data when possible
 - a) Data for each area/site
 - b) Secondary attack rates as above
3. Immune data
 - a) Antibody levels from each bleed
 - b) Cellular immune markers
4. Rodent data

Thank you



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