An R&D Blueprint for action to prevent epidemics

Lassa Fever Vaccine Trials Design

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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.

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. Maybe 10% of HCW’s. 5-7% SAR

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, but maybe up to 10%

In countries and regions with transmission, transmission is fairly common, with seroprevalence up to 60%. More serosurveys are needed.
Lassa – target population for vaccine

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.
Lassa – target 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 considerations

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

iRCT in geographic clusters in areas mapped to have transmission.
Lassa in Nigeria

Seasonal transmission in Nigeria with a large outbreak now

- 2016: 109 confirmed cases
- 2017: 143 confirmed cases
- 2018 (so far): 365 confirmed and >1000 suspected
Lassa – important considerations

Screening at baseline

Bleed all of the trial participants before vaccination, and probably exclude them if they are seropositive, OR

Plan for a stratified analysis on initial 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 PCR choose the right one!
Co primary or secondary Severe disease at lower boundary

**Secondary endpoints**
- Infection needs Ab detection and if GP vaccine use NP ELISA to distinguish....
- Stratified analyses on prior immune measures exploratory?
- Stratified analyses on different lineages and/or clades (sieve analysis) exploratory?
- 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: 
\[
\overline{VE} = 1 - \frac{\hat{\lambda}_1}{\hat{\lambda}_0}
\]

- \( \hat{\lambda}_1 \) = estimated hazard of illness for individuals who receive vaccine.
- \( \hat{\lambda}_0 \) = estimated hazard of illness for individuals who receive placebo.

One-sided hypothesis test for the primary outcome:

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

Secondary analyses using same setup

Statistical method: Cluster-stratified, Cox proportional hazards model, with appropriate \( \alpha \) – spending for interim analyses.
Testing more than one vaccine

More than one session
Defined follow up period per subject

• e.g., two vaccines would be randomized in a 1,1,1 pattern or 2,2,2 need to review/consider as an option
• NEED 2 placebos....
Individual randomization within sites

One protocol

Multiple sites including consider multi national

\[ VE = 1 - \frac{\lambda_1}{\lambda_0} \], combined across the n sites as stratification or regression
Sample Size for Primary Outcome With One Vaccine split alpha in two end points then need 90 and 44 events if VE 70 per cent need to revisit all numbers split the alpha among é vaccines????

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

<table>
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<th>VE</th>
<th>Average required total # of events</th>
<th>Cumulative attack rate in placebo arm</th>
<th>Cumulative attack rate in vaccination arm</th>
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<th>Sample size in vaccination arm</th>
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Problem: Combining information across outbreaks

Any single outbreak may be too small to adequately power an entire vaccine efficacy trial.

Incomplete results from underpowered trials may be misleading to decision-makers.

We recommend a proactive strategy for planning to combine information across outbreaks.
Solution:

1. SINGLE Master protocol
   • Can be single or multi-center
   • Preferred approach

2. Prospective meta-analysis
   • If master protocol is not possible
“Master protocol” approach

Conventional trial with a protocol that stops and starts with outbreaks

If the trial does not achieve the targeted number of events in the first outbreak, the study remains blinded to allow for further data collection.

Interim analyses to assess efficacy or futility can be timed to occur at the end of each outbreak (or after reaching a target number of events).
“Prospective meta-analysis” approach

Where timing of next outbreak is unpredictable, keeping data blinded is not acceptable

If incomplete study results are revealed for each trial, they can be combined in a meta-analysis—most useful if pre-planned with coordination across trials in data collection.

This requires the least coordination, but does not preserve type I error control, but can be quite useful in clarifying efficacy
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
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
Thank you