

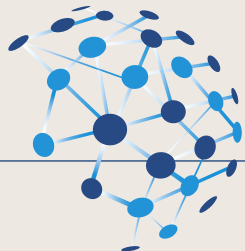
Trial design

Lassa Fever

Vaccines

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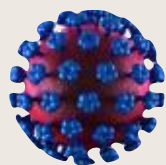
Co- Lead WHO R&D Blueprint for epidemics



R&D Blueprint

Powering research
to prevent epidemics

Global level



Lassa

Critical path for research and potential use
Criteria for candidate products prioritization
Dashboard progress (Taskforce)

Roadmap
Jan 2018

Non product
research
WHE/GOARN...

TPP
Vax 2017
Dx – April 2018
Tx – April 2018

Dashboard of
candidate
products vs TPPs
R&D Observatory

CORE
Protocols Designs
Vx- June 2018
Tx – April 2018
Dx – FIND May
2017

No. of doses for Phase 2b/3 trials
Site selection
Modelling
Method. discussion

Deployment
(outside trials)
2018

EUAL or SAGE or R&D Blueprint
recommendations
Global coordination plan
Access to candidate products

Mapping of
stakeholders

WHO
expert
Groups

Recommendations
priority research
during event

WHE/IMS

Country
Operational
Emergency Plan

Country level

NRAs + ERCs - AVAREF joint reviews of protocols - established

Support to countries for liability and compensation - available

Tools for review/design of trials at country level - available

Tools for data sharing and sample sharing- MTA

Surveillance, lab, case management, ...

NRA or NITAG recommendations
Trained teams, logistics
National coordination plan
Community engagement
Access to candidate products



R&D Blueprint
Powering research
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Lassa fever – trial design considerations

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

Index-case driven, **iRCT** with placebo in geographic clusters in areas mapped to have transmission.

The clusters could be households, villages and/or clinics and hospitals containing the index case or cases.



Lassa fever –Ascertainment of cases

Suspected case

Illness with gradual onset with one or more of the following: malaise, fever, headache, sore throat, cough, nausea, vomiting, diarrhoea, myalgia, chest pain hearing loss and a history of contact with excreta of rodents or with a case of Lassa Fever

Confirmed case

A suspected case that is laboratory confirmed (positive IgM antibody, PCR or virus isolation) or epidemiologically linked to a laboratory confirmed case

Lassa fever – target population for vaccine

Non-emergency setting (Preventive Use):

Populations living in **areas where Lassa virus is endemic.**

HCW at particularly high risk of LF due to their profession

Emergency setting (Reactive/Outbreak use):

Protection of **at-risk persons in the area of an ongoing outbreak** for the prevention of LF as well as to interrupt chains of virus transmission and to terminate outbreaks.

A reactive use vaccine will be very useful if a large outbreak occurs, potentially in a new/unexpected setting, with extensive human-to-human transmission.

Lassa fever – target population

Options:

Healthy adults and children, excluding pregnant and lactating women

(or also include pregnant and lactating women)

Lassa fever – end point considerations

Primary endpoint

Infection or clinical disease?

Considering the low pathogenicity of 20%, as detected with PCR or seroconversion

Secondary endpoints

Clinical disease

Death

Lassa fever –considerations

Screening at baseline

Blood 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 fever –correlates of protection*

Measuring clinical and pre-clinical immunogenicity will require validated and standardized assays.

- Based on animal studies, both neutralizing antibodies and cell-mediated immunity appear to have a role in preventing LASV infection.
- Immune markers demonstrating vaccine effectiveness appear to be different across vaccine platforms.
- These studies indicate that LASV specific antibody; neutralizing antibodies and markers of cell-mediated immunity will need to be tested.

* as noted in the TPP

Combining information across outbreaks & trials

For diseases with sporadic and unpredictable (and often small) outbreaks, information can be accumulated across trials in time and space

Each new outbreak provides more information towards the VE estimators

If iCRT then shorter time, quicker results (fewer cluster/people needs to be vaccinated).

Care must be taken with α -spending, blinding for analysis, and comparability of risk in clusters as more are added

There are various methodological challenges including choice of comparator and issues related to α -spending and interim analyses

Observational studies

Case-control studies, test-negative control

For each case, one or more matched controls are selected

- Test negative = draw controls from negative Lassa infect tests
- Standard case control = draw controls from same communities, matched on occupation, etc.

Requires a population with high but partial vaccine coverage (recommended <90%)

One arm study

A prospective cohort with unvaccinated participants (e.g. ineligible or non-consenting)

Comparator selection is an issue, Statistical methods will be challenging

Need to adjust for key confounders,

But, could potentially provide additional evidence

Observational studies

Case-control studies, test-negative control

There are various methodological challenges including choice of comparator and issues related to confounding as this is not randomised although issues of confounding are may be of lower concern when high efficacies are expected

One arm study

There are various methodological challenges as before, in addition most robust estimates will be available when vaccine is highly effective



World Health
Organization

Thank you



R&DBlueprint

Powering research
to prevent epidemics

The power of coordinating global research

The Constitution of the World Health Organization (WHO) defines that one of WHO's key roles is to promote, conduct and coordinate research in the field of health.



By embedding research at the heart of the pandemic response we can achieve two goals: to help end the acute phase of the current pandemic and protect us from the epidemics and pandemics of the future.



Tedros Adhanom
Director-General,
World Health Organization (WHO)