Considerations on Case Definitions and Potential Objectives & Endpoints

Workshop on Accelerating the Licensure of Lassa Vaccines
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Lassa Fever Case Definition in ENABLE study

- Case definition to be used and validated in the ENABLE epidemiology study
- High sensitivity, suitable for active / passive case detection
- Severity of disease not differentiated in the incident case definition

1. Acute febrile illness case:

Self reported fever >48 hours (2 consecutive nights) + 1 sign/symptom listed below

Signs and symptoms associated with Lassa fever disease	
Headache	Abnormal bleeding (mouth, nose, rectum and/or vagina)
Cough	Oedema of neck and face
Vomiting	Conjunctival/sub-conjunctival haemorrhage
Chest pain	Buzzing in ears or acute deafness
Sore throat	Spontaneous abortion
Abdominal pain	Jaundice
Muscle pain or Joint pain	Hypotension

2. Confirmed Lassa fever clinical disease:

Acute febrile illness case + positive Lassa RT-PCR

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CEPI (2020)Lassa fever generic Protocol, ENABLE Lassa fever cohort study, 25

Alternative Lassa Fever Case Definition

- Similar to case definitions previously used e.g. in phase 3 vaccine efficacy trials for dengue and Ebola ring vaccination trials

1. **Acute febrile illness case:**

Febrile illness on any 2 of 3 consecutive days (≥ 38°C) or illness clinically suspected to be Lassa Fever by the investigator

2. **Confirmed Lassa fever clinical disease case:**

Acute febrile illness case + positive Lassa RT-PCR

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Henao Restrepo AM et al., Lancet 2017; Biswal S et al., NEJM 2019; Villar L et al., NEJM 2015

Primary Objective/Endpoint to Consider for Lassa Vaccine Phase 3 Clinical Trial

Objective	Endpoint
• Evaluate vaccine efficacy against confirmed Lassa fever (LF) of any severity / any lineage occurring 14 days after last dose in all trial participants	• Cumulative incidence based on RT-PCR confirmed LF clinical disease of any severity, due to any LASV strain, with or without serological evidence of past Lassa virus (LASV) infection

- Efficacy against LF clinical disease due to 'any strain' is relevant from a public health perspective
- Enrolment of all-comers – secondary analyses to be stratified by serostatus at baseline
- Based on preliminary ENABLE data up to ¼ of trial subjects will be seropositive at baseline
  - Dependant on definite Phase 3 trial population

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Potential Secondary Objectives/Endpoints to Consider for Lassa Vaccine Phase 3 Clinical Trial (1/3)

Objectives	Endpoints
CLINICAL	
• Evaluate vaccine efficacy against confirmed LF of any severity / any lineage occurring 14 days after last dose **without evidence of infection before vaccination**	• Cumulative incidence based on PCR-confirmed LF clinical disease irrespective of disease severity, due to any LASV strain, without serological evidence of past LASV infection
• Evaluate vaccine efficacy against confirmed LF of any severity / any LASV lineage occurring 14 days after last dose **with evidence of infection before vaccination**	• Cumulative incidence based on PCR-confirmed LF clinical disease irrespective of disease severity, due to any LASV strain, with serological evidence of past LASV infection
• Evaluate vaccine efficacy against confirmed LF of any severity **separately for lineages** occurring 14 days after last dose stratified by presence / absence of evidence for previous infection	• Cumulative incidence based on PCR-confirmed LF clinical disease irrespective of disease severity, separately for LASV strains, in all as well as baseline seropositives / seronegatives

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Potential Secondary Objectives/Endpoints to Consider for Lassa Vaccine Phase 3 Clinical Trial (2/3)

Objective	Endpoint
CLINICAL	
• Evaluate vaccine efficacy against **severe LF** (TBD), any lineage, occurring 14 days after last dose stratified by presence / absence of evidence for previous infection	• Cumulative incidence based on PCR-confirmed LF clinical disease meeting criteria of severe disease (TBD), due to any LASV strain, in all as well as baseline seropositives / seronegatives
• Evaluate vaccine efficacy against **hospitalisation due to LF**, any lineage, occurring 14 days after last dose stratified by presence / absence of evidence for previous infection	• Cumulative incidence based on PCR-confirmed LF clinical disease in trials participants hospitalised for LF clinical illness, due to any LASV strain, in all as well as baseline seropositives / seronegatives
• Evaluate vaccine efficacy against confirmed LF of any severity / any lineage occurring **immediately** after last dose in all trial participants	• Cumulative incidence based on RT-PCR confirmed LF clinical disease of any severity, due to any LASV strain, with or without serological evidence of past LASV infection

Potential Secondary Objectives/Endpoints to Consider for Lassa Vaccine Phase 3 Clinical Trial (3/3)

Objective	Endpoint
IMMUNOLOGIC (immunogenicity subset)	
• Assess post vaccination immune response based on binding antibodies (bAbs) against LASV glycoprotein	• Seropositivity rate (SPR): Percentage of participants with measurable serum IgG levels to LASV glycoprotein by ELISA 28 days after last dose • Seroconversion rate (SCR): Percentage of participants, 28 days after last dose, with ➢ measurable serum IgG in baseline seronegatives or ➢ 2-fold serum IgG titre increase in baseline seropositives • Geometric mean fold rise (GMFR): fold change of GMTs at baseline versus 28 days after last dose
• Assess post vaccination immune response based on neutralizing antibodies (nABs) against LASV	• Seropositivity rate (SPR): Percentage of participants with measurable serum nAb (wild-type or pseudo virus assay, TBD) levels to LASV 28 days after last dose • Seroconversion rate (SCR): Percentage of participants, 28 days after last dose, with ➢ measurable serum nAb in baseline seronegatives or ➢ 2-fold serum nAb titre increase in baseline seropositives • GMTs at 28 days after last dose

Seropositive @ baseline = measurable anti-GP bAb prior to 1st dose

Potential Exploratory Objectives to Consider for Lassa Vaccine Phase 3 Clinical Trial

- Cellular immune response incl. T-/B-cell memory
- Long-term protection against hospitalisation
- 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 participant to analyse breakthrough cases)
- Other?

Further Stratifications for Consideration

- Gender (m / f)
- Age (TBD in line with trial population age range)
- Country
- Time post vaccination (short-term, intermediate term, long-term - TBD)
- Other?

Discussion Points

- Trial population **age range**
- Post vaccination **immune response assessment** in a subset of participants (but collect serum samples from ALL subjects to enable subsequent CoP analyses in LF cases)?
  - Humoral (binding Abs, neutralising Abs)
  - CMI (incl. memory)
- Definition **baseline seropositivity**: anti-GP bAbs versus nAbs / lineage-specific assessments?
- Baseline seropositivity testing (IgG only?) in **every subject for secondary objectives**?
- Include prevention of "death" as a secondary endpoint
- **Long-term VE**: Shall the VE trial be split into **2 phases** – similar to dengue VE trials:
  - Part 1 (active phase) = active LF case detection until 12 months post completing primary immunisation in each individual trial participant
  - Part 2 (passive phase) = participants hospitalised for LF until End of Study, e.g. 3 years after last-subject-in (LSI)
- **Malaria testing** in every suspected every LF case and referral for treatment
- Other?

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