Selected regulatory questions related to Lassa fever vaccines

Phil Krause

Consultant to WHO

Study success criteria

- Criteria for licensure of a vaccine require substantial evidence of efficacy
- Regulators often request two independent clinical trials, or one trial with very strong results
- For vaccines, a single trial is normally sufficient if the lower bound on the 95% confidence interval for efficacy is at some level meaningfully above zero
- For COVID vaccines, the lower bound was set at 30%, due to the importance of understanding efficacy in the context of a pandemic when many vaccines were studied at once
- For other licensed vaccines, lower bounds between 0 and 30% have been used
- Vaccine efficacy against severe disease is expected to exceed efficacy against mild disease
- Clinical endpoint trials are essential given difficulty of identifying immune correlates of protection

Considerations related to TPP and duration of protection

- We don’t currently know duration of vaccine protection
- A preventive vaccine would ideally protect for several years, while a reactive vaccine could succeed if protection lasts one season
- If the trial needs to continue for more than one season, and vaccine-induced protection were to wane, a reactive vaccine that would be effective in an outbreak setting might not succeed in the trial
- Attack rates in subsequent years will likely be lower, reducing trial efficiency after year 1
- The season is short, and it will be important to collect cases efficiently
- A trial of a vaccine used in a reactive mode, ideally one that can be completed in one season, could address both types of vaccine
- Implications:
  - identify areas of transmission early in the season and vaccinate quickly to collect as much data as possible in the first season
  - Only evaluate one vaccine at a time in order to have the best chance to get useful data

Implications of multiple lineages

- Clinical trials will likely address efficacy against a small number of lineages
- Ideally the trial would be geographically broad and cover many lineages
- How will we know that vaccine will be effective against other lineages?
  - If vaccine is not well matched to lineages in study, the clinical study might be considered a "worst case"
    - It would likely be possible to show that immune responses against other lineages are similar to or better than those against the lineages tested in the study
  - If vaccine is well-matched to lineages in the study, we won't have direct data on less well matched lineages, and immune responses to less well matched lineages may be weaker
    - It will be important to know immune responses to all important lineages before starting the phase 3 study
  - To the extent we rely on immune assays for these determinations, we will need to have confidence that the assays are measuring the right thing, and that they are reliable
    - Monoclonal antibodies can be protective, but CMI is critically important
    - Because CMI antigens are simpler, protection mediated by CMI may be retained even if humoral responses are weaker

Safety considerations

- Lassa fever pathogenesis is incompletely understood
- To the extent that some aspects of disease may be immune-mediated, there is a theoretical possibility that they could be caused by a vaccine
- It will be important to closely observe trial participants and collect robust safety data with specific attention to any potential adverse events that are seen as part of Lassa fever

Possible development pathway

- Early phase studies to collect initial safety data, determine immune responses to all relevant strains
- Additional safety data could potentially be obtained with larger early phase studies or by incorporating intensive safety follow-up in phase 3 trial
- Efficacy trial- ideally single season if feasible
  - Enroll participants in areas where disease incidence is likely to be high
- Overall safety database for licensure needs to be adequate
- Lot consistency
  - Part of safety study
  - Part of efficacy study
  - Might not be needed if manufacturing process is well-controlled

Regulatory questions

- What should be the lower bound on the 95% confidence interval to show success?
- How much safety data should be obtained before proceeding to phase 3? Can some of the phase 2 safety data be collected in early stages of a phase 3 study, or would it be better to collect it before phase 3 (e.g., off-season)?
- Are there other strategies or considerations to gain confidence that a vaccine will work against all lineages?