An R&D Blueprint for action to prevent epidemics

Plague Vaccine Trials Design

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What we have learned since 2018 about trail design (slide added)


Plague – target population for vaccine

Reactive/ emergency use

– Protection of at-risk people in the area of an active outbreak of plague. Clusters of transmission.

Preventive/ prophylactic use

– Populations living in areas where plague is endemic.

– Health care workers (HWCs) at particularly high risk of plague due to their profession.
Plague – target population

Options:

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

(or also include pregnant and lactating women)
Plague – vaccine trial design considerations

A prospective, randomized, double-blind, placebo-controlled (or delayed comparator), efficacy trial

iRCT in geographic clusters in areas mapped to have transmission.
Plague – Madagascar, 2017

- 2348 confirmed, probable and suspected cases, about 500 confirmed
- 1791 cases of pneumonic plague, of which 22% were confirmed, 34% were probable, and 44% were suspected
- 341 cases of bubonic plague, one case of septicaemic plague
- 215 cases with type unspecified.

Plague – endpoint considerations

Primary endpoint
Laboratory-confirmed plague clinical illness, for all types of plague

Secondary endpoints
• Laboratory-confirmed bubonic plague
• Laboratory-confirmed pneumonic plague
• Death
• Immunological correlates of risk and surrogates of protection, i.e., surrogates for VE
Statistical analysis

The primary analysis will be the estimated vaccine efficacy against confirmed plague illness: \( \overline{VE} = 1 - \hat{\theta} \), where \( \hat{\theta} = \frac{\lambda_1}{\lambda_0} \)

- \( \hat{\lambda}_1 = \) 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 (slide added)

- We can test $m$ products against a single (shared when possible) placebo arm.

<table>
<thead>
<tr>
<th>Time Window #1</th>
<th>Time window #2</th>
<th>Time window #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine arms</td>
<td>A</td>
<td>AA</td>
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<tr>
<td></td>
<td></td>
<td>BB</td>
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<tr>
<td>Placebo arms</td>
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<td>$P_B$</td>
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<tr>
<td>: shared-placebo</td>
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**Randomization scheme.** Candidate vaccine A and its matched placebo $P_A$ enter the trial in time window #1. In this example, Vaccine A utilizes the combined placebo arms ($P_A$, $P_B$ and $P_C$) from all three-time windows. Vaccine B and its matched placebo $P_B$ enter in time window #2. In this example, Vaccine B utilizes the combined placebo arms from time windows #2 ($P_A$ and $P_B$) and #3 ($P_A$, $P_B$ and $P_C$). Vaccine C and its matched placebo $P_C$ enter in time window #3. In this example, Vaccine C utilizes only the placebo arms ($P_A$, $P_B$ and $P_C$) from time window 3.
Individual randomization within sites

Multiple sites/outbreaks

1  2  ……………….……  n

Sites  Enrolled participants within sites

VE = 1 - \( \frac{I_{vacc}}{I_{unvacc}} \), 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

<table>
<thead>
<tr>
<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>
<th>Sample size in placebo arm</th>
<th>Sample size in vaccination arms</th>
<th>Total sample size</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. Core (change from “master”) protocol
   - Can be single or multi-center
   - Preferred approach

2. Prospective meta-analysis
   - If core protocol is not possible
“core 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)
Flow for combing (hypothetical)

Outbreak #1 starts; Trial #1 starts

Outbreak #1 ends; interim analysis conducted

Trial #1 stop for futility (low conditional power)

Trial #1 stop for efficacy

Trial #1 results inconclusive

Decision to preserve blinding of data
Outbreak #1 starts; Trial #1 starts

Outbreak #1 ends; interim analysis conducted

Trial #1 stop for futility (low conditional power)

Trial #1 stop for efficacy

Trial #1 results inconclusive

Decision to preserve blinding of data

Outbreak #2 starts; Trial #2 starts

Outbreak #2 ends; interim analysis conducted

Trial #2 stop for futility (low conditional power)

Trial #2 stop for efficacy

Trial #2 results inconclusive

Decision whether to merge Trial #1 and Trial #2
The case of plague vaccine trials

Reactive/emergency use

• If another large pneumonic outbreak occurs in Madagascar (or elsewhere), then a single season should prove enough cases to assess VE, otherwise two seasons will probably be needed

Preventive/prophylactic 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