An R&D Blueprint for action to prevent epidemics

Plague Vaccine Trials Design

World Health Organization

University of Florida
Plague – basic facts for vaccine trial design

• Currently, the three most endemic countries are the Democratic Republic of the Congo, Madagascar, and Peru
• Plague can be a very severe disease in people, with a case-fatality ratio of 30% to 60% for the bubonic type, and is always fatal for the pneumonic kind when left untreated
• Antibiotic treatment is effective against plague bacteria, so early diagnosis and early treatment can save lives.
• Bubonic plague is transmitted between animals and humans by the bite of infected fleas, direct contact with infected tissues
• Pneumonic through inhalation of infected respiratory droplets
Plague – basic facts

Incubation period:
- 2-6 days bubonic
- 1-3 days pneumonic

Pathogenicity:
- high, maybe close to 100%?

For pneumonic plague

Serial interval:
- ≈ 5 days

Human Basic Reproductive number: $R_0 \approx 3$
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

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

A prospective, randomized, double-blind, placebo-controlled, 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
• 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: 

$$\overline{VE} = 1 - \hat{\theta}, \text{ where } \hat{\theta} = \frac{\lambda_1}{\lambda_0}$$

- $\lambda_1 = \text{estimated hazard of illness for individuals who receive vaccine.}$
- $\lambda_0 = \text{estimated hazard of illness for individuals who receive placebo.}$

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

• We can test $m$ products against a single placebo arm, using Bonferroni or a more complex correction for $\alpha$
• e.g., two vaccines would be randomized in a 1,1,1 pattern with two hypothesis tests, each at $\alpha = 0.025$
Individual randomization within sites

Multiple sites/outbreaks

\[ VE = 1 - \frac{I_{vacc}}{I_{unvacc}}, \] 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>
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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>
<th>Sample size in placebo arm</th>
<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. **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)
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
"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.
The case of plague vaccine trials

Reactive/emergency use
• If another large pneumonic outbreak occurs in Madagascar (or elsewhere), then a single season should proved 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