WHO Consultation on Plague: What R&D progress has been achieved and how can we accelerate development of a vaccine?

Animal model challenges: How to evaluate response after infection and vaccination?

October 12, 2023
Good news, bad (?) news…

- We have good, reproducible animal challenge models and assays
  - Antibiotics FDA approved through Animal Rule
  - Assays utilized in animal studies and clinical trials

- The challenge is in equating animal protection to human protection, complicated by the relative contributions of humoral and cellular immunity, which differs amongst vaccines and/or species
  - We lack a true correlate of protection
Yersinia pestis, CO92

- Isolated from a fatal case of primary pneumonic plague in a 31yo male exposed to a cat who died within minutes of being carried from a crawlspace with symptoms consistent with plague

- Medial lethal dose, LD$_{50}$
  - Cynomolgus macaque, 66 cfu aerosol
  - African Green monkey, 343 cfu aerosol
  - Mouse, 68,000 cfu aerosol
    - 45 cfu intraperitoneal; 426 cfu intranasal
  - Rat, 1600 cfu, aerosol
    - 250 cfu intranasal

- Human infective dose, estimated at 100-500 cfu
## Disease Comparison: Human to NHP

<table>
<thead>
<tr>
<th>Feature</th>
<th>Human</th>
<th>African Green</th>
<th>Cynomolgus Macaque</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time course</td>
<td>2 to 9 days</td>
<td>2 to 9 days</td>
<td>2 to 9 days</td>
</tr>
<tr>
<td>Temperature</td>
<td>Elevated in 100% of cases</td>
<td>Elevated in 100% of cases</td>
<td>Elevated in 100% of cases</td>
</tr>
<tr>
<td><em>Y. pestis</em> present</td>
<td>Positive in 100% of sputum</td>
<td>Positive in 100% of blood and/or lung/nasal fluid</td>
<td>Positive in 100% of blood</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Pulmonary infiltrates</td>
<td>Pulmonary infiltrates</td>
<td>Not done</td>
</tr>
</tbody>
</table>
## Disease Comparison: Human to NHP (2)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Human</th>
<th>African Green Macaque</th>
<th>Cynomolgus Macaque</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung pathology</td>
<td>Consolidations, Inflammatory infiltrates, Hemorrhagic/frothy fluid, Exudates and effusions, Bronchopneumonia, Bacilli</td>
<td>Bacteria, Pulmonary congestion, Necrohemorrhagic foci, Inflammatory infiltrates, Pleural fibrin, Mediastinitis</td>
<td>Bacteria, Pulmonary congestion, Necrohemorrhagic foci, Inflammatory infiltrates, Pleural fibrin, Mediastinitis</td>
</tr>
</tbody>
</table>
Natural History of Pneumonic Plague, AGM

![Graph showing respiratory rate, heart rate, and temperature trends over time.](image-url)
Vaccinated Cynos return to baseline

![Graph showing baseline return of vaccinated Cynos](image)
Bridge ELISAs

- Species independent
- Plate is coated with antigen (F1, V, F1V)
- Then incubated with test sera
- Biotinylated antigen, streptavidin-conjugated enzyme and chromogenic substrate are added, rather than using species-specific reagents
- Calibrated against curve of chicken IgY standards
Vaccine Protection, Cynomolgus Macaque

a) Probability of Survival vs. Log₁₀ (Bridge ELISA Titer rF1V)

- Logistic Model
- 95% Fieller's Interval
- Non-Survivors
- Survivors

b) Probability of Survival vs. Vaccine Dosage (µg)

- Logistic Model
- 95% Fieller's Interval
- Animal Results
# Antibiotic survivors seroconvert (cyno)

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment, post-fever</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>doxy @ 5hrs</td>
<td>7 of 8</td>
</tr>
<tr>
<td>2</td>
<td>cipro @ 5hrs</td>
<td>4 of 4</td>
</tr>
<tr>
<td>3</td>
<td>placebo @ 5hrs</td>
<td>0 of 4</td>
</tr>
<tr>
<td>4</td>
<td>doxy @ 15hrs</td>
<td>6 of 8</td>
</tr>
<tr>
<td>5</td>
<td>cipro @ 15hrs</td>
<td>6 of 6</td>
</tr>
<tr>
<td>6</td>
<td>placebo @ 15hrs</td>
<td>0 of 4</td>
</tr>
</tbody>
</table>

![Graph showing rF1 ELISA result over time](image-url)
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Questions?

Thank you!

jhewitt@nih.gov