

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?**

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Infectious Diseases

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# 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

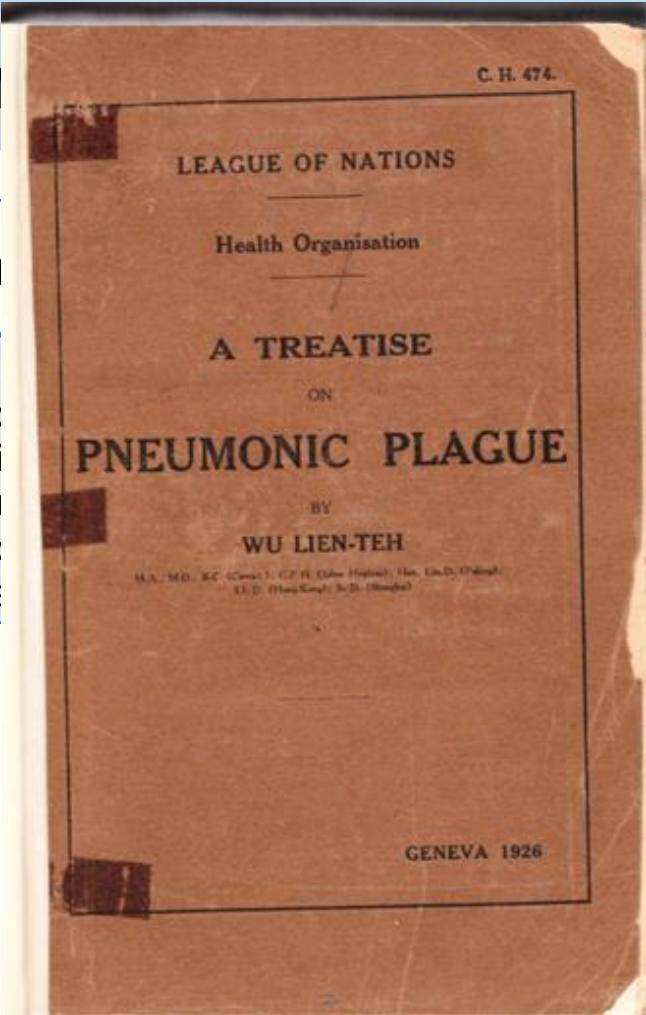
- Isolated from a fatal case of primary pneumonic plague in a 31yo male exposed to a cat who died within minutes of being carried from a crawlspace with symptoms consistent with plague
- Medial lethal dose, LD<sub>50</sub>
  - Cynomolgus macaque, 66 cfu aerosol
  - African Green monkey, 343 cfu aerosol
  - 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

Feature	Human	African Green	Cynomolgus Macaque
Time course	2 to 9 days	2 to 9 days	2 to 9 days
Temperature	Elevated in 100% of cases	Elevated in 100% of cases	Elevated in 100% of cases
<i>Y. pestis</i> present	Positive in 100% of sputum	Positive in 100% of blood and/or lung/nasal fluid	Positive in 100% of blood
Heart rate	Elevated	Elevated	Elevated
Respiratory rate	Elevated	Elevated	Elevated
Chest radiograph	Pulmonary infiltrates	Pulmonary infiltrates	Not done

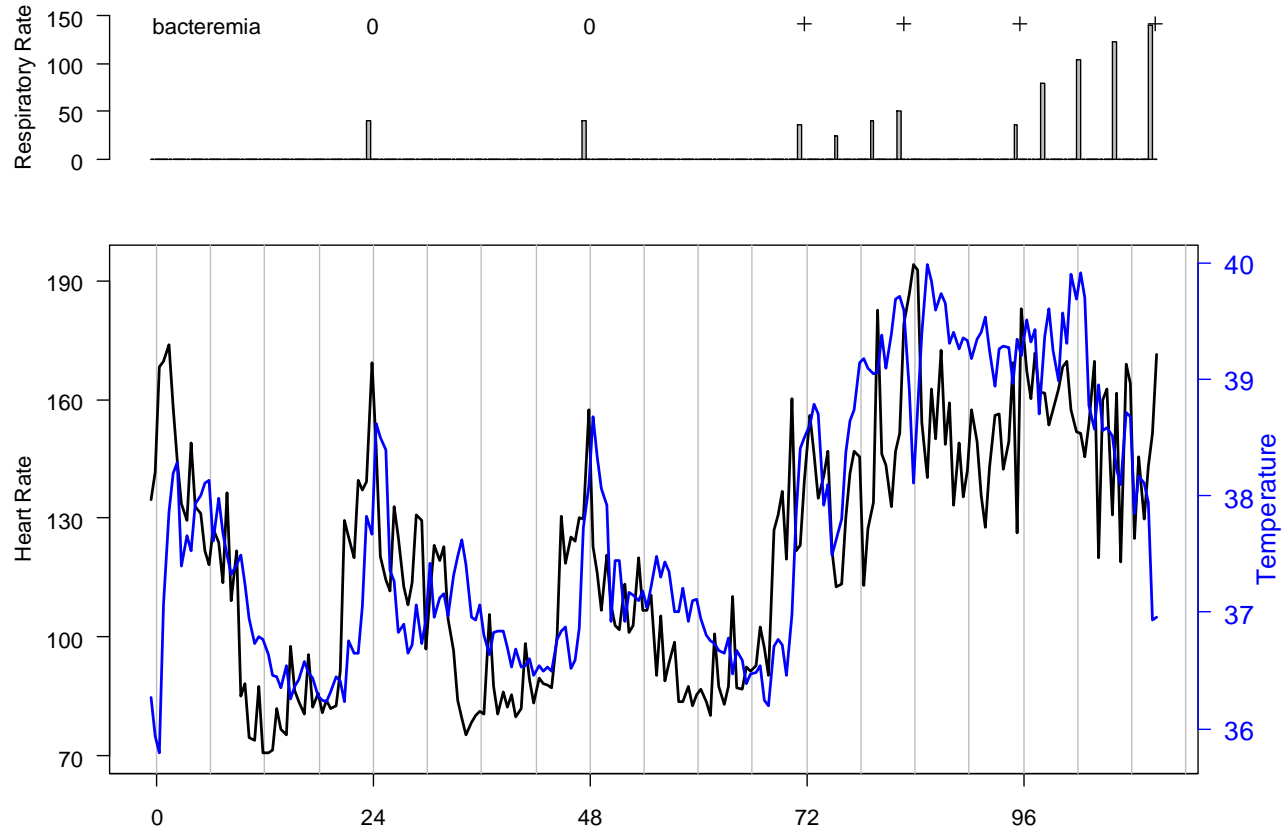
# Disease Comparison to NHP (2)

Feature	Human
Lung pathology	Consolidation Inflammation Hemorrhagic Exudates and Bronchopneumonia

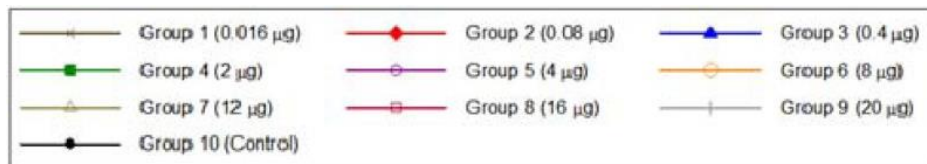
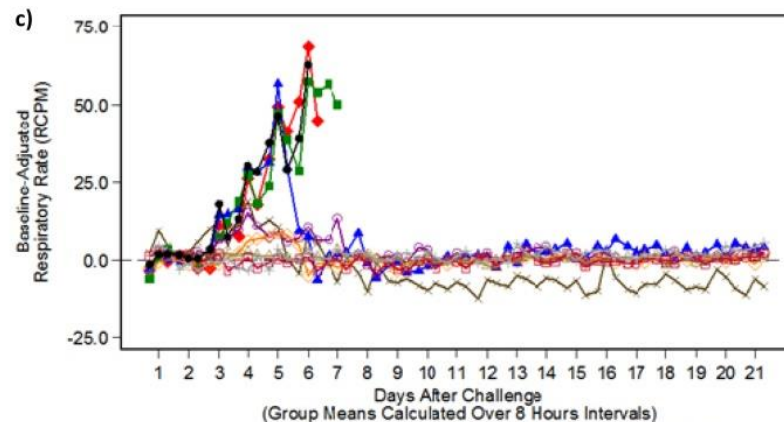
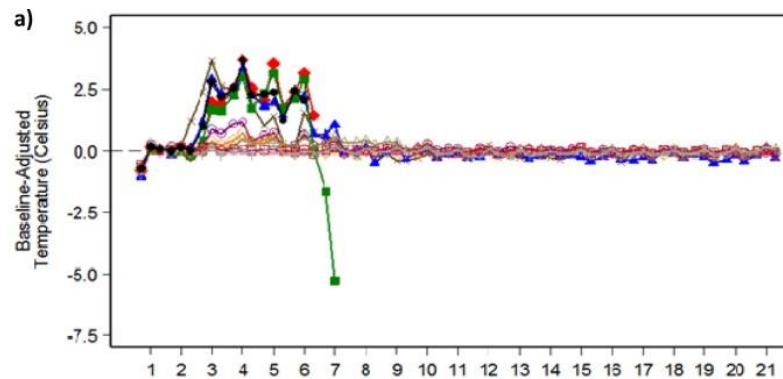


	Cynomolgus Macaque
	Bacteria, Pulmonary congestion, Necrohemorrhagic foci, Inflammatory infiltrates, Pleural fibrin, Mediastinitis

# Natural History of Pneumonic Plague, AGM

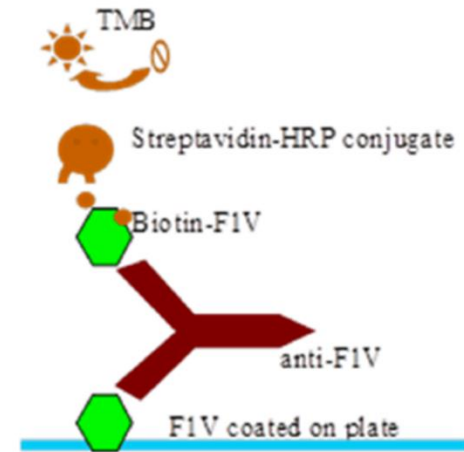


# Vaccinated Cynos return to baseline



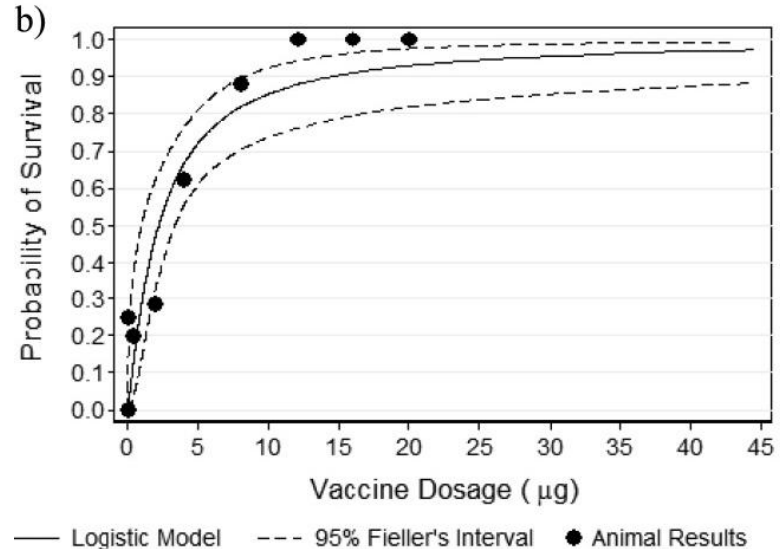
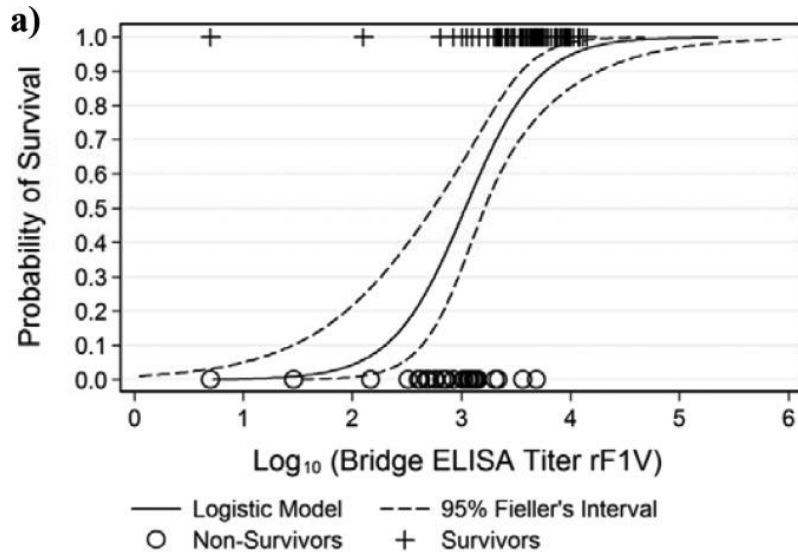
# Bridge ELISAs

- Species independent
- Plate is coated with antigen (F1, V, F1V)
- Then incubated w/ 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



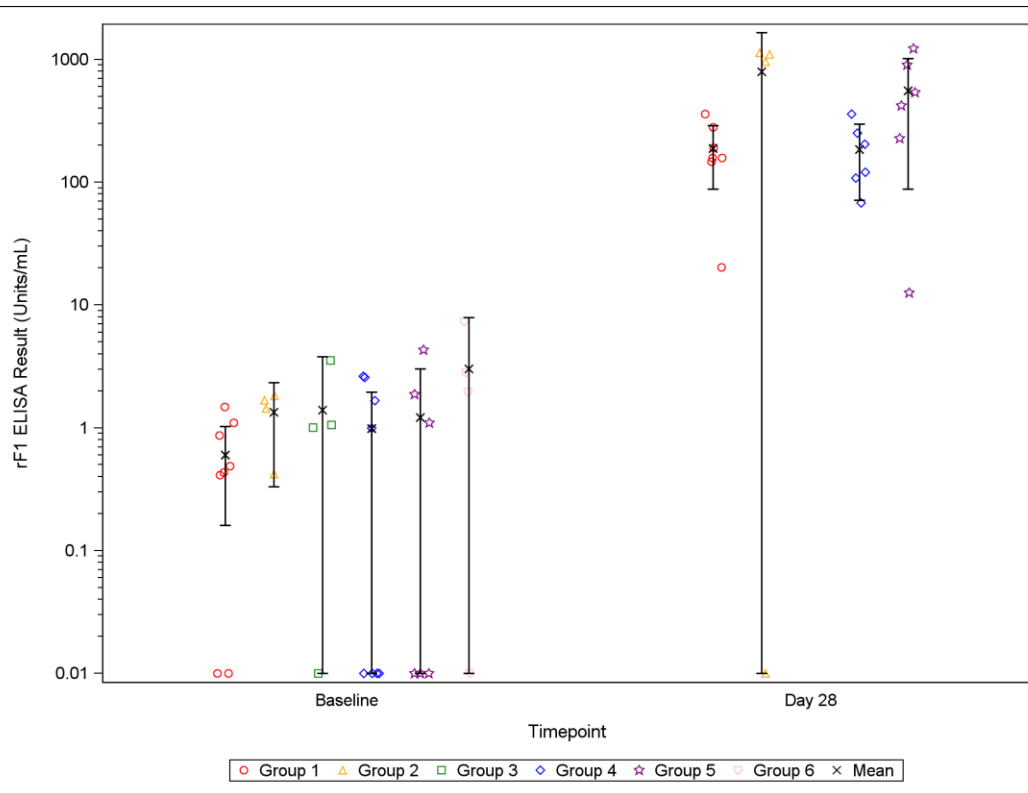


# Vaccine Protection, Cynomolgus Macaque



# Antibiotic survivors seroconvert (cyno)

Group	Treatment, post-fever	Survival
1	doxy @ 5hrs	7 of 8
2	cipro @ 5hrs	4 of 4
3	placebo @ 5hrs	0 of 4
4	doxy @ 15hrs	6 of 8
5	cipro @ 15hrs	6 of 6
6	placebo @ 15hrs	0 of 4



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# Questions?

*Thank you!*