Our vision is a U.S. Military Force that has a full medical countermeasure capability to fight and win in any CBRN battlespace worldwide.

rF1V Plague Vaccine

WHO Workshop "Efficacy trials of Plague Vaccines: endpoints, trial design, site selection"

Presented to:

World Health Organization

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MCS
MEDICAL COUNTERMEASURE SYSTEMS

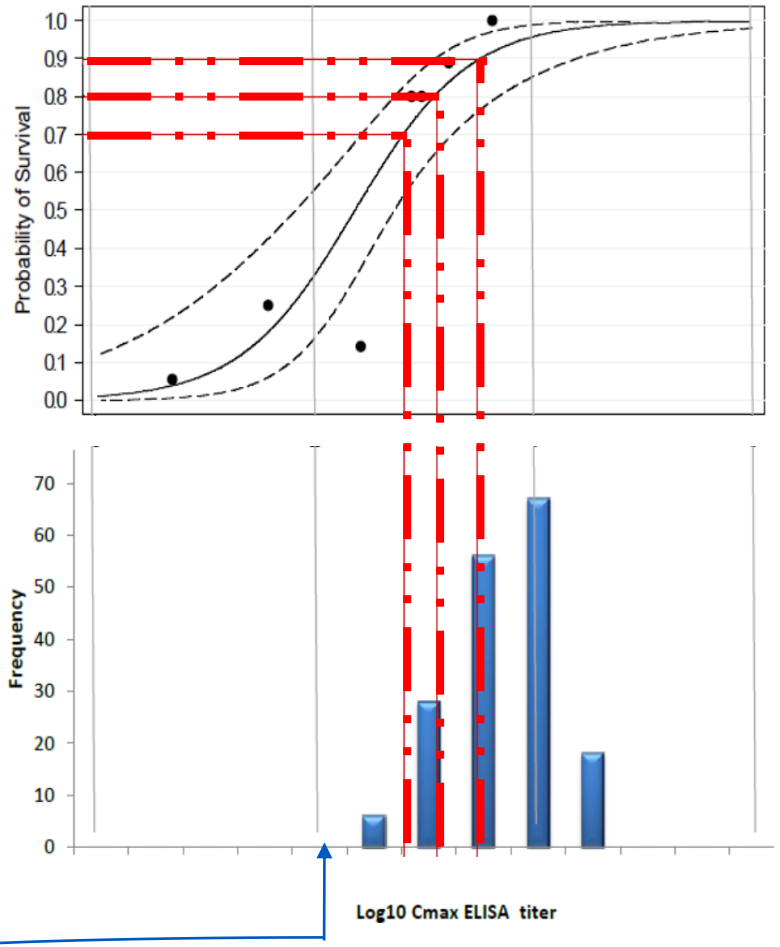
rF1V Plague Vaccine Target Product Profile

- **rF1V is a subunit vaccine composed of recombinant *Y. pestis F1* capsular & V proteins formulated in aluminum adjuvant**
  - F1 subunit sufficient for prevention of bubonic disease; V subunit sufficient for protection against pneumonic disease
- **Indication:** For the protection of adults 18 to 55 years of age against pneumonic plague caused by aerosol exposure to *Y. pestis*
- **Three dose regimen (0.5 mL per dose) administered intramuscularly on days 0, 28 & 182 (6 month schedule); annual boosters thereafter**
- **Storage at 2-8 C in single dose vials; vial shelf-life at 5+ years (ongoing)**
- **Vaccine efficacy and conferred clinical benefit data being generated per FDA guidance related to US Code of Federal Regulations Title 21 CFR 314.600 - 314.650 (drugs) or 21 CFR 601.90 - 601.95 (biological products), commonly referred to as the "FDA Animal Rule" (New Drug and Biological Products; Evidence Needed to Demonstrate Efficacy of New Drugs When Human Efficacy Studies are Not Ethical or Feasible)**

Mary Kate Hart, George A. Saviolakis, Susan L. Welkos, and Robert V. House, "Advanced Development of the rF1V and rBV A/B Vaccines: Progress and Challenges," Advances in Preventive Medicine, vol. 2012, Article ID 731604, 14 pages, 2012. doi:10.1155/2012/731604

Bridging Animal Efficacy to Vaccine Immunogenicity under Animal Rule

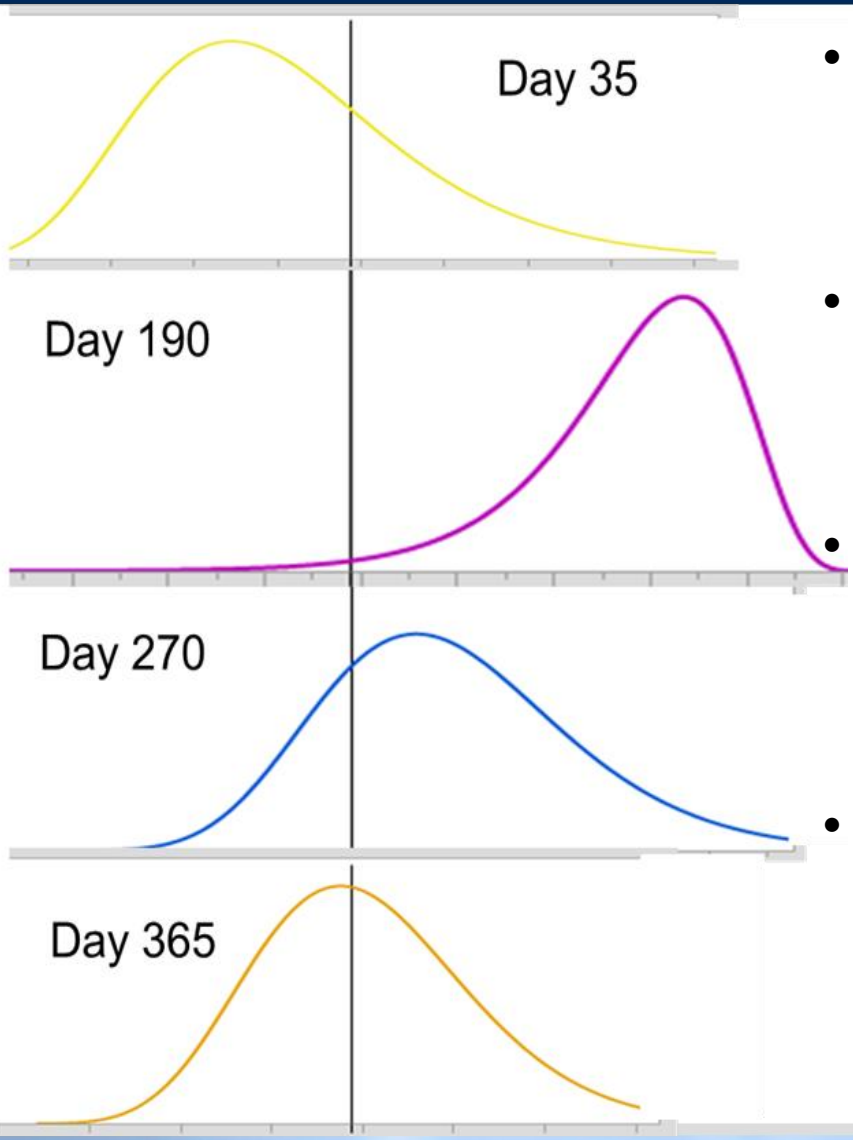
- **Top Right: Survival curve from AR efficacy studies completed to date**
  - Y axis = % NHP surviving high dose aerosol *Y. pestis* exposures as predicted by their serum rF1V ELISA titer at time of challenge
  - X axis = Log10 serum rF1V ELISA titer
- **Bottom Right: Frequency (Y axis) of Phase 2 subjects with differing ranges (blue bars) of serum rF1V ELISA titers (X axis) at 1-3 weeks post immunization with 3rd rF1V vaccine dose**
- **Red dotted-dashed lines depict the "bridge" for rF1V ELISA titers in sera from vaccinated subjects to the same titer in sera from vaccinated NHPs to determine predicted efficacy under Animal Rule for a given vaccine-induced rF1V ELISA titer**



NOTE: For Animal Rule licensure, >90-95% of all Phase 3 subjects receiving vaccine must develop rF1V ELISA titers above this pre-determined value negotiated with the FDA

L Burns, Drusilla. (2012). Licensure of vaccine using the Animal Rule. Current opinion in virology. 2. 353-6. https://doi.org/10.1016/j.coviro.2012.01.004

Kinetics of Protective Immunity per Animal Rule post-rF1V Vaccination



- **Day 35:** A portion of adult subjects (e.g. 22-25%) already develop rF1V ELISA titers above the minimal (threshold) Animal Rule (AR)-predicted protective immunity levels after dose 2 (yellow line)
- **Day 190:** Virtually all (e.g. >99%) adult subjects develop AR-predicted protective immunity following the third dose with the majority of titers at levels bridging to NHP efficacies above 80% (purple line)
- **Day 270:** The AR-predicted protective immunity as measured by the rF1V ELISA starts to wane in a portion of subjects (e.g. 20-25%) after 3 months post-vaccination to levels below that negotiated with the FDA for licensure (blue line)
- **Day 365 (or 1 year post first dose):** The rF1V ELISA titers in subjects continue to wane and level off around 1 year post-initial vaccination with about half of the subjects above & half below the protective antibody level for licensure and identifies need for/timing of the booster immunization (gold-brown line)

Kinetic Modelling courtesy of Dr. Kevin Wingerd, MCS-JVAP

Relating R_0 to Vaccine Efficacy

- The relationship between R_0 and impact on vaccine efficacy is described below, where P_c (e.g. vaccine efficacy) is the critical percentage of immune individuals required to achieve population herd immunity

$$P_c = 1 - \frac{1}{R_0}$$

- The R_0 for transmission of pneumonic plague has been estimated to be 0.96 - 2.3*

$$\text{If } R_0 = 2.3 \longrightarrow 1 - \frac{1}{2.3} = 0.57$$

- Consequently, vaccines which elicit protective immunity against pneumonic plague disease in $\geq$ 57% of a population have the greatest potential to ascertain rapid burn out and/or control-prevention of pneumonic plague outbreaks in endemic areas

*From Gani R, Leach S. Epidemiologic Determinants for Modeling Pneumonic Plague Outbreaks. Emerg Infect Dis. 2004;10(4):608-614. https://dx.doi.org/10.3201/eid1004.030509

Summary

- **In 'plague-naïve' populations:**
  - rF1V vaccine, in 3 doses IM over 6 months, is predicted to confer immunity against pneumonic plague in >98% of vaccinated subjects
  - Approximately ¼ of plague-naïve subjects have developed AR-protective immunity to pneumonic plague after 2 doses and within 5 weeks post first dose
  - By 6 months post-full vaccination regimen, about ½ of subjects showed rF1V ELISA titers waning below our pre-determined threshold for licensure suggesting need for annual boosters to maintain AR-predicted protective immunity in a naïve population
- **Performance data for rF1V vaccine support its use for the control and prevention of pneumonic plague among persons in endemic disease areas**

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