National Institute of Allergy and Infectious Diseases

Developing an Animal Model of Pneumonic Plague

FDA Workshop

March 1, 2017

NIAID

National Institute of Allergy and Infectious Diseases

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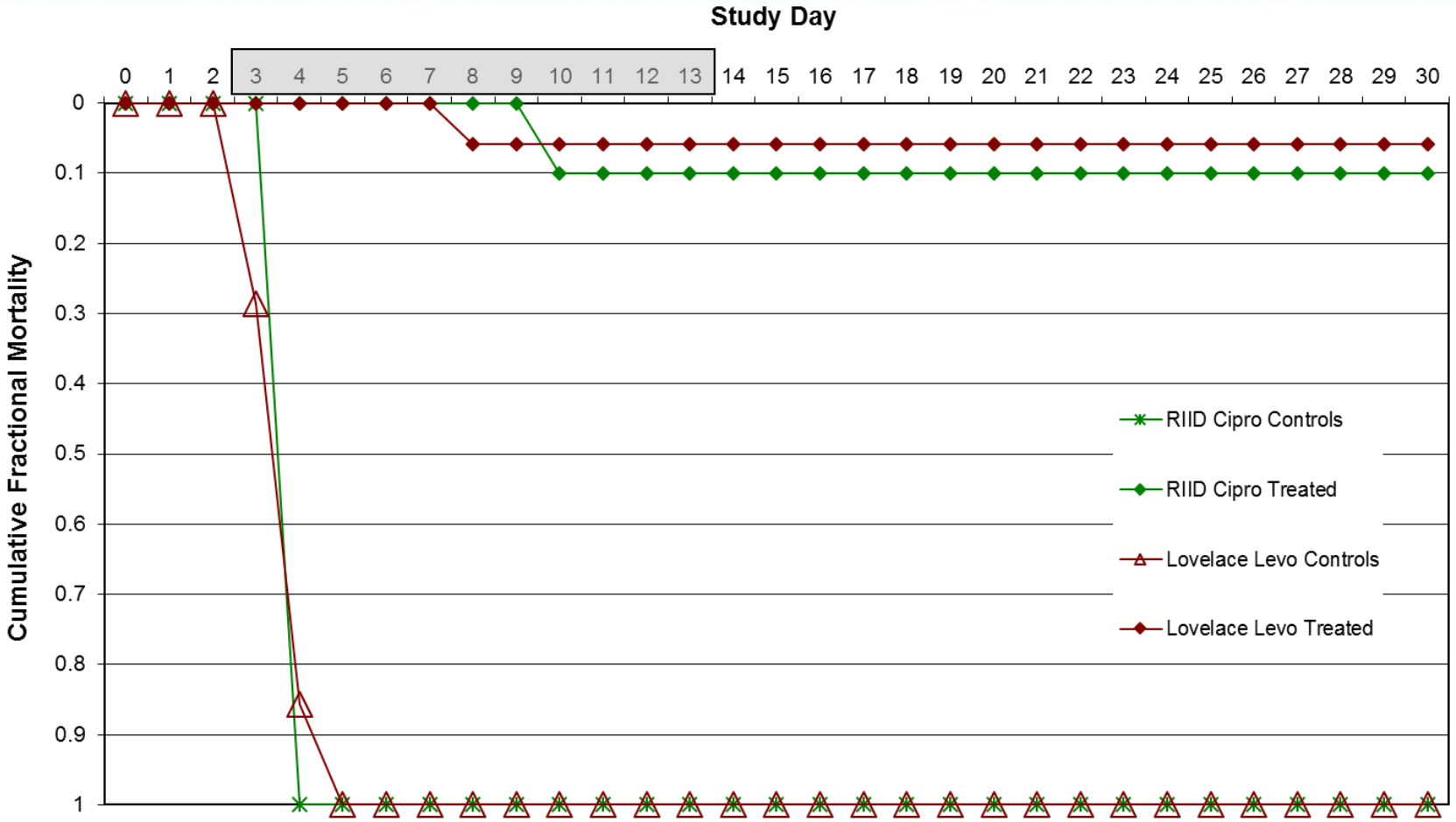
Office of Biodefense, Research Resources, and Translational Research (OBRRTR)

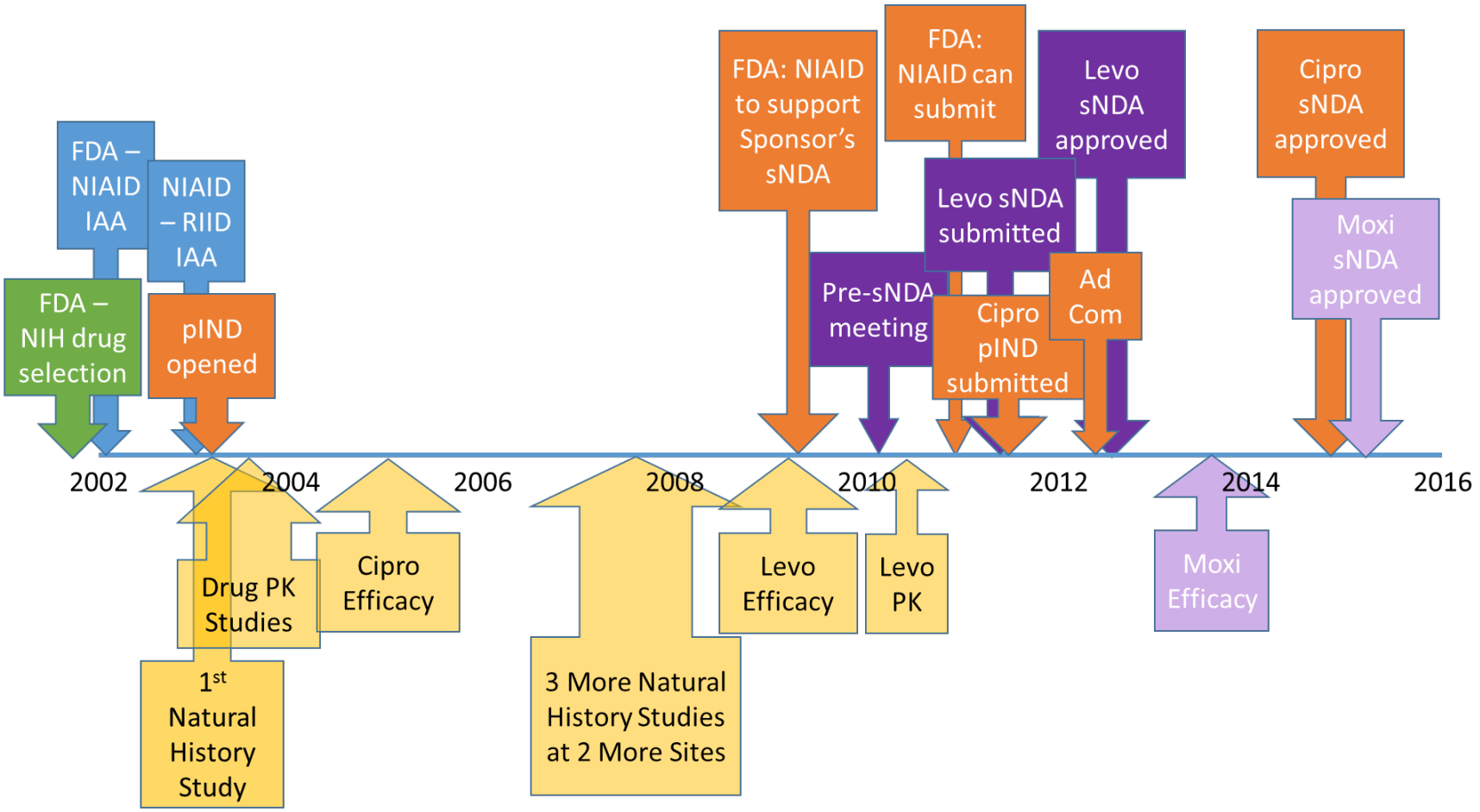
Disclaimer

- I am a federal employee.
- I receive no external funding.
- I am presenting only federally funded work.
- My opinions are mine and do not necessarily represent those of the NIAID/NIH.

Pneumonic Plague Treatment Efficacy of Two Fluoroquinolones



Timeline



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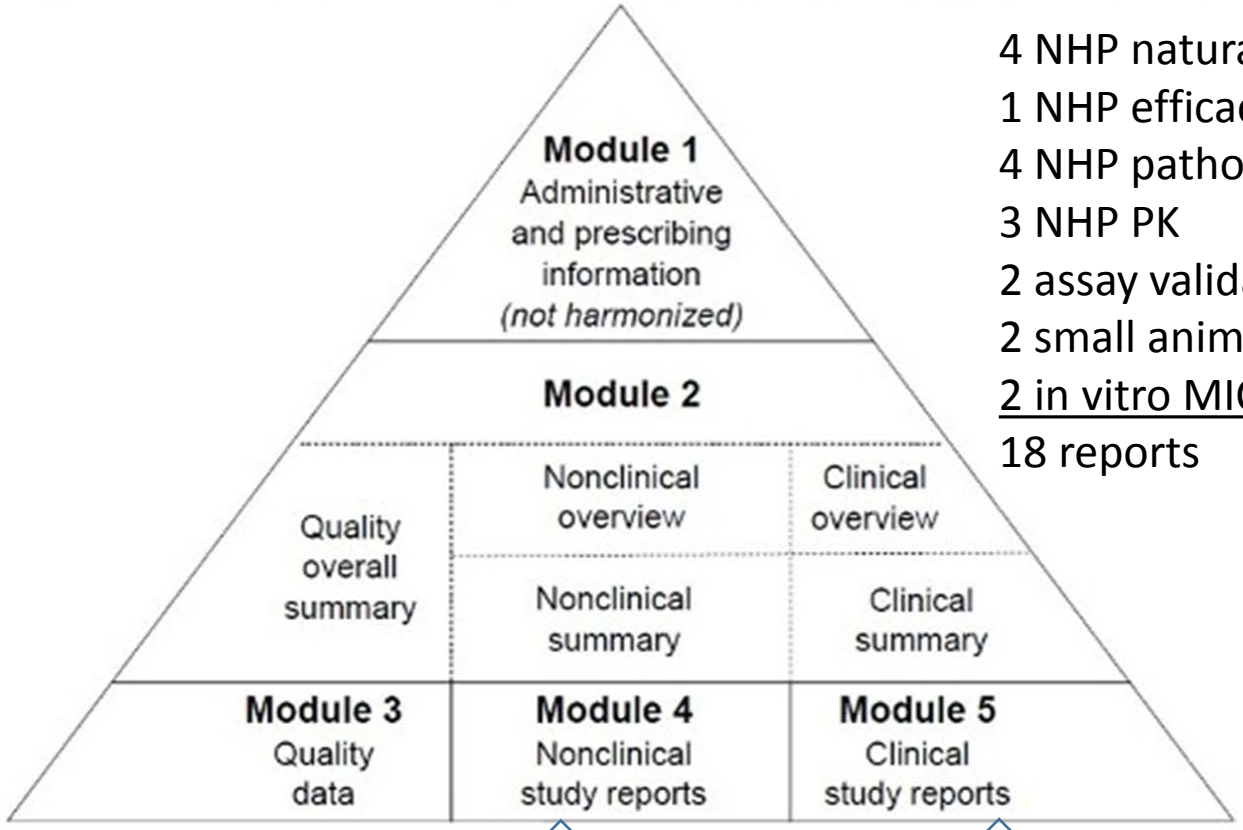
sNDA Submission: 400 MB, >250 files



4 NHP natural history
1 NHP efficacy
4 NHP pathology/radiology
3 NHP PK
2 assay validation
2 small animal efficacy
2 in vitro MIC
18 reports

79%: 18 reports, 64 refs, datasets

19%: 1 white paper, 70 refs

African Green Monkey (AGM) Natural History Studies

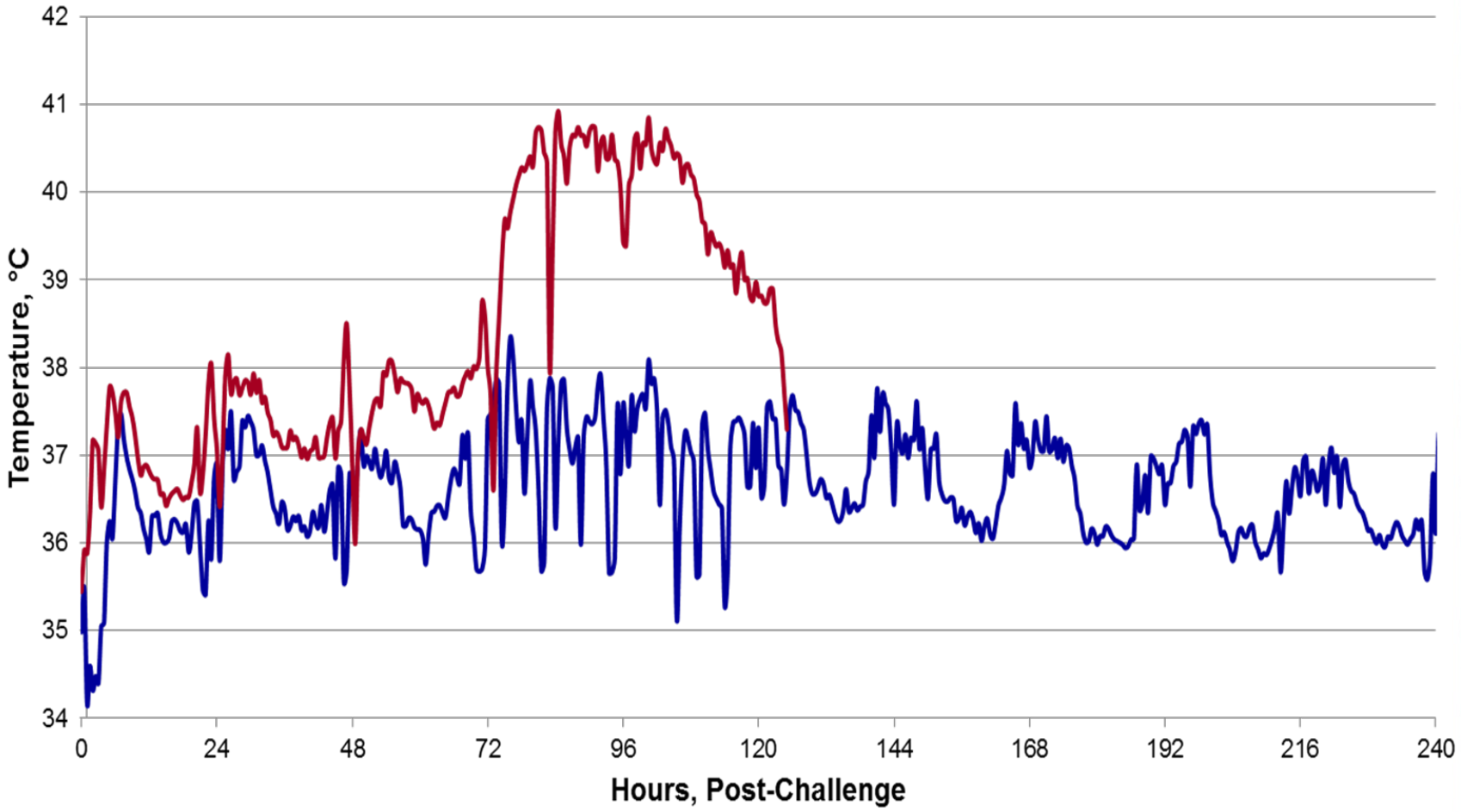
Study, Site	Number of Animals	Challenge Dose, LD_{50}	Mean Time to Death, hours	Mortality	# Bacteremic/ # Febrile
F03-09G, USAMRIID	3 M, 3 F	25.3 ± 17.3	111.8 ± 10.4	4/6	4/4
FY06-126, Lovelace	5 M, 5 F	134.7 ± 68.1	90.1 ± 10.0	10/10	10/10
617, Battelle	3 M, 7 F	613.7 ± 386.1	72.8 ± 11.1	10/10	10/10
875, Battelle	5 M, 5 F	48.1 ± 23.1	93.3 ± 21.3	10/10	10/10
Overall	36 (16 M, 20 F)			34/36 (94%)	34/34

Bacteremia

Animal	Inhaled Dose, LD_{50}	Time (hours)						
		24	48	72	80	83	96	Terminal cfu/ml (hr)
V627	57	-	-	+	nd	+	+	$8x10^7$ (111.5)
V514	30	-	-	+	+	nd	+	$3x10^6$ (111)
V569	23	-	-	+	nd	+	+	$9x10^8$ (99.5)
V113	21	-	+	+	nd	+	+	$1x10^8$ (125)
V521	12	-	-	-	nd	nd	-	nd
V605	9	-	-	-	nd	nd	-	nd

+ = growth; - = no growth; nd = not done

Body Temperature, Survivor vs. Non-Survivor



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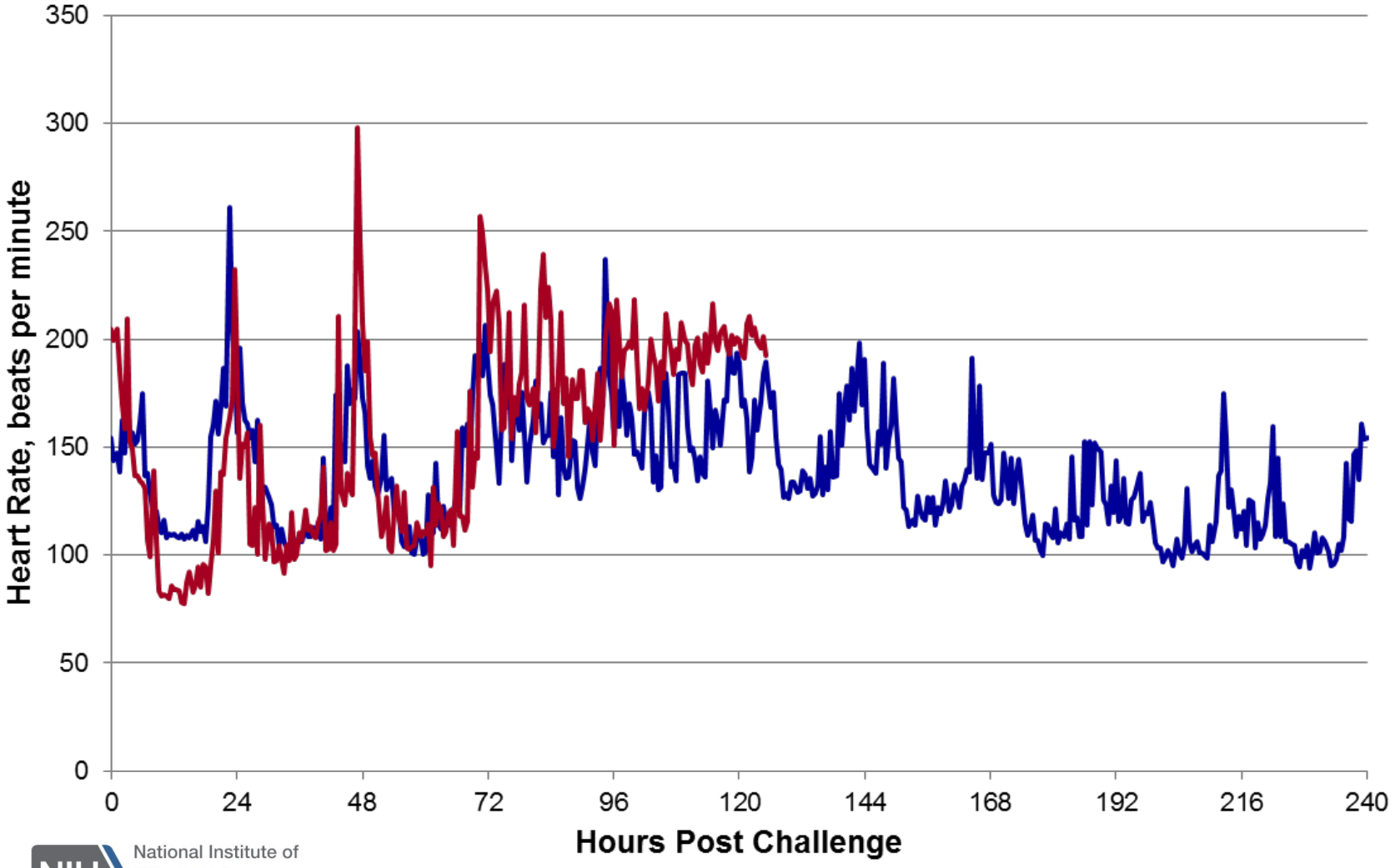
Heart Rate, Survivor vs. Non-Survivor



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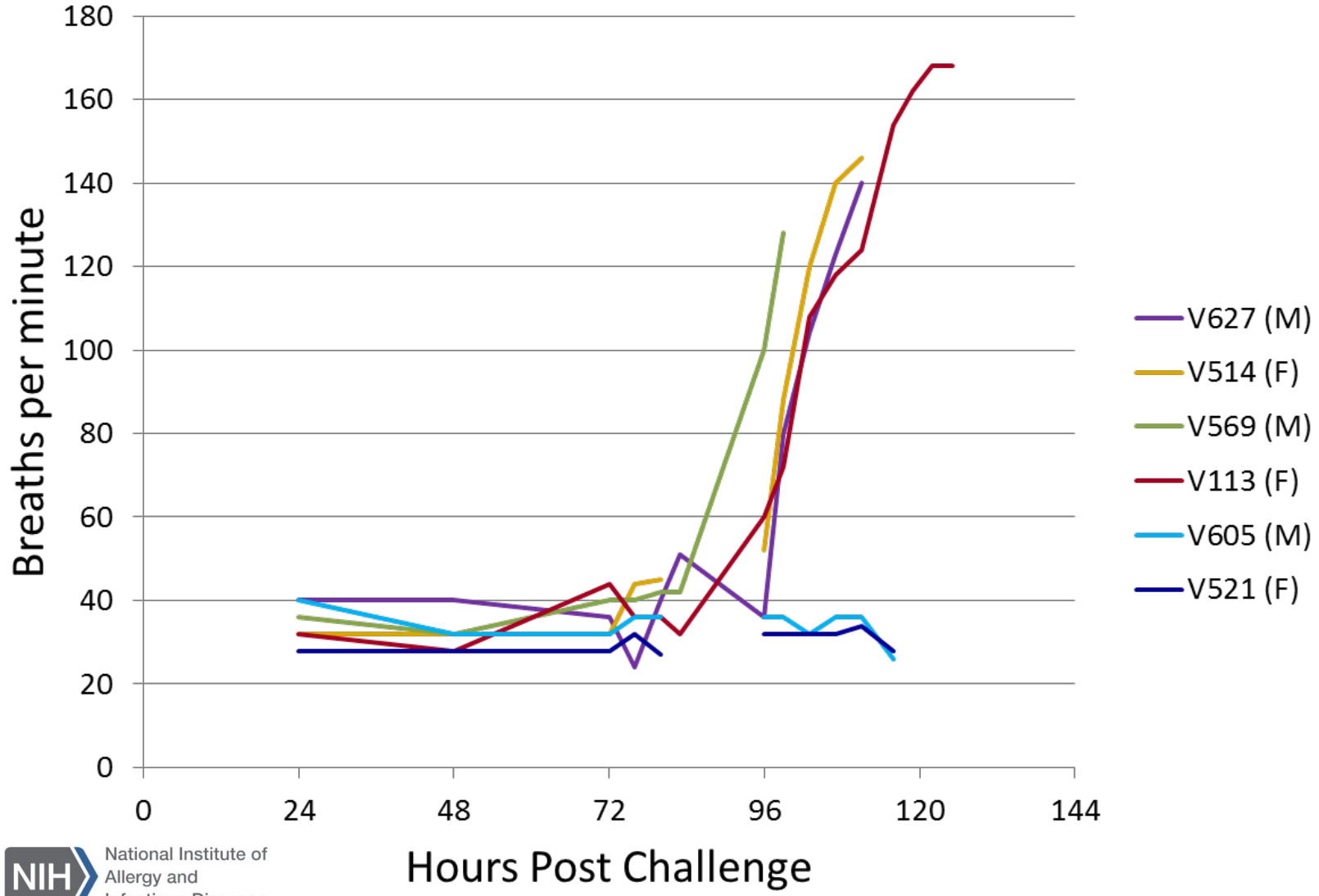
Respiratory Rate



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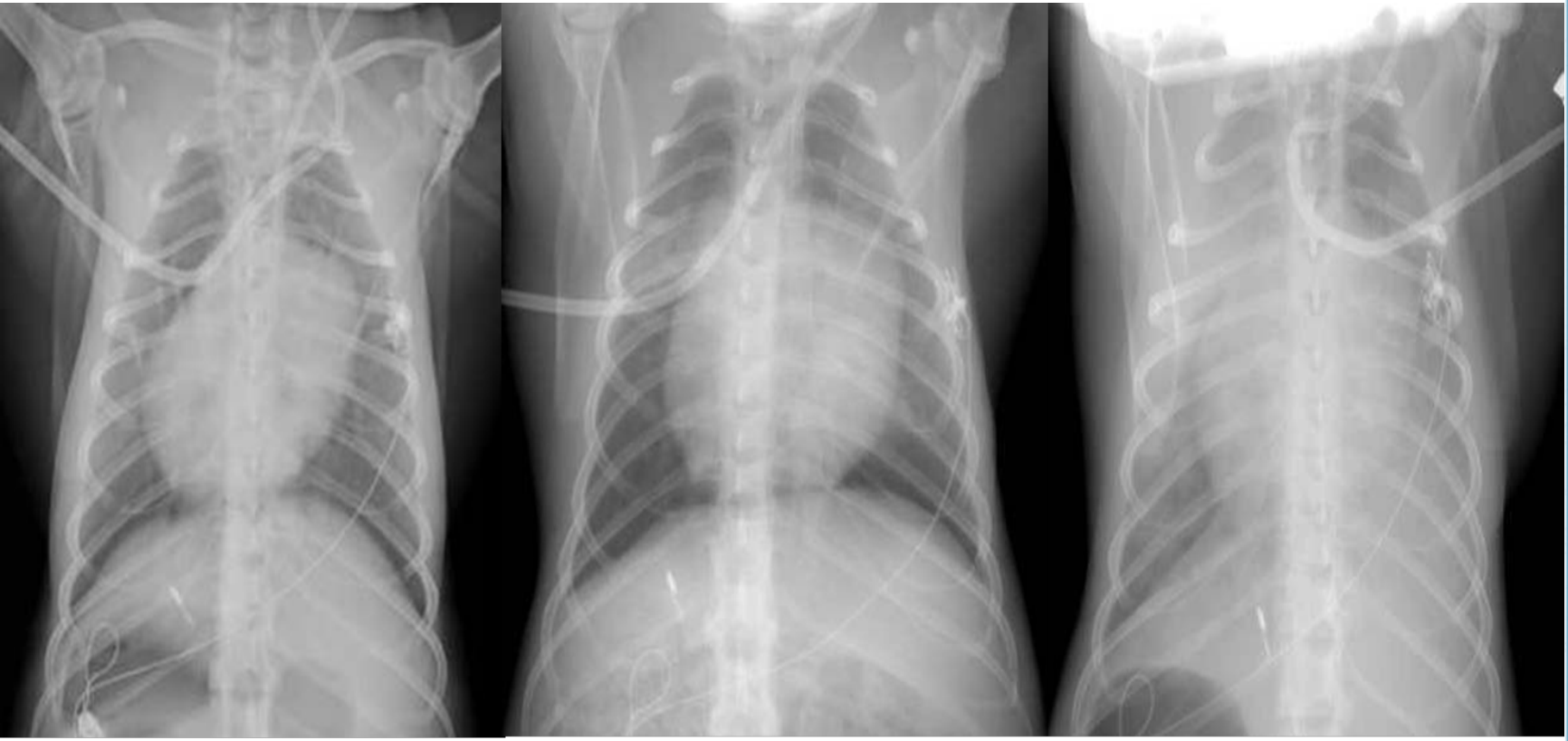
Chest Radiographs



0 hr

83 hr

111.5 hr

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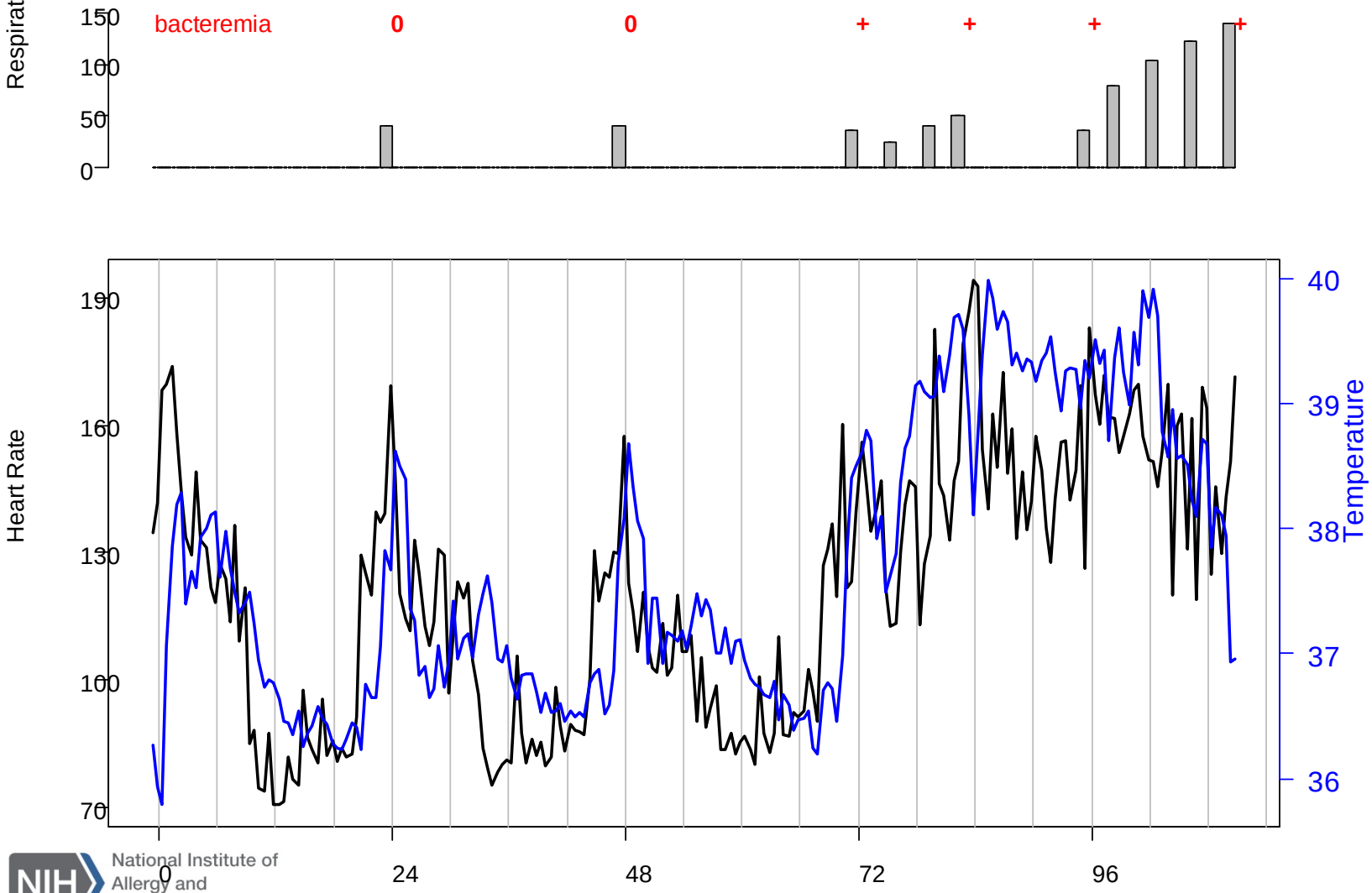
Individual Animal Endpoint Profile



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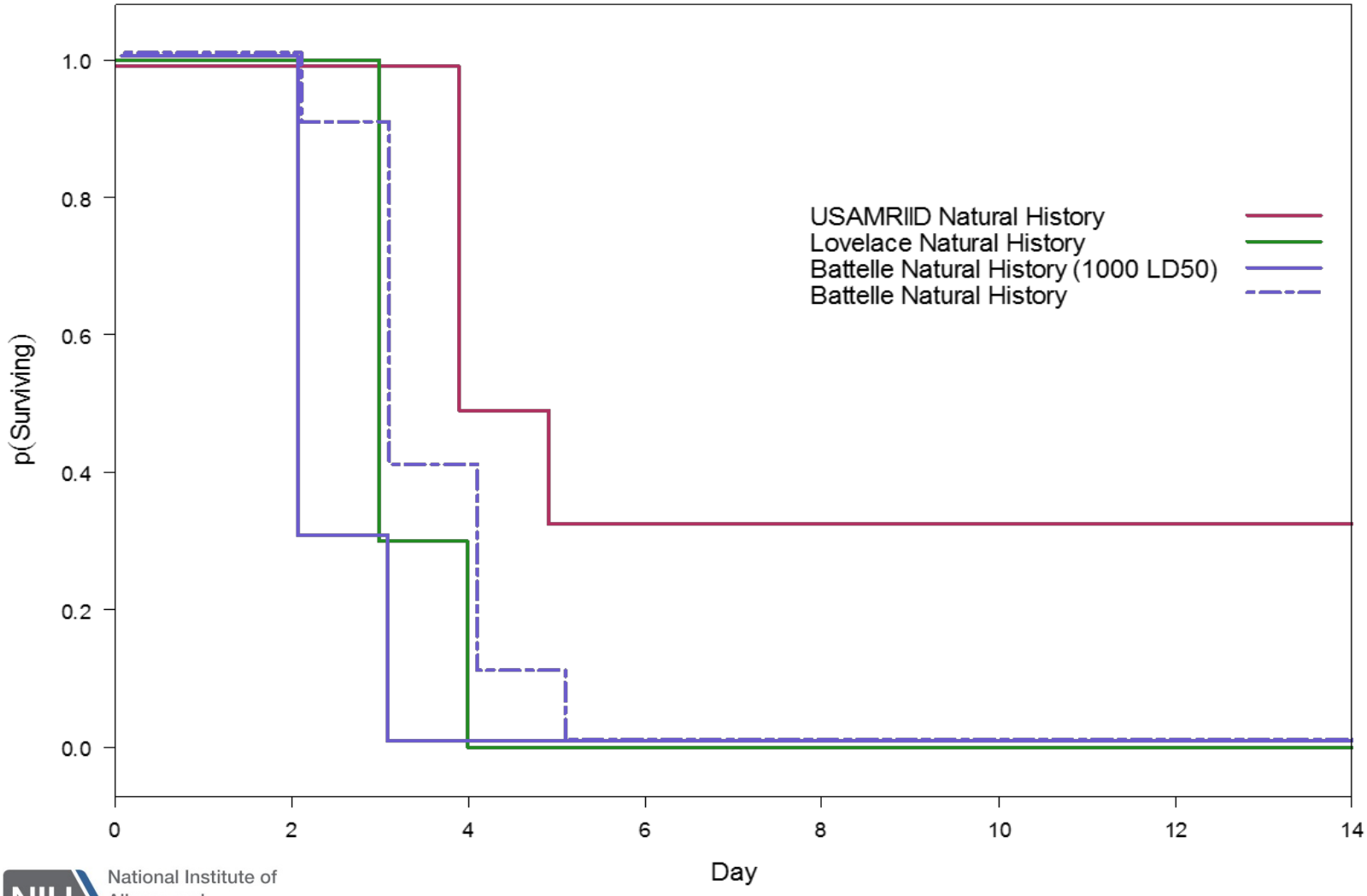
Survival, across Studies



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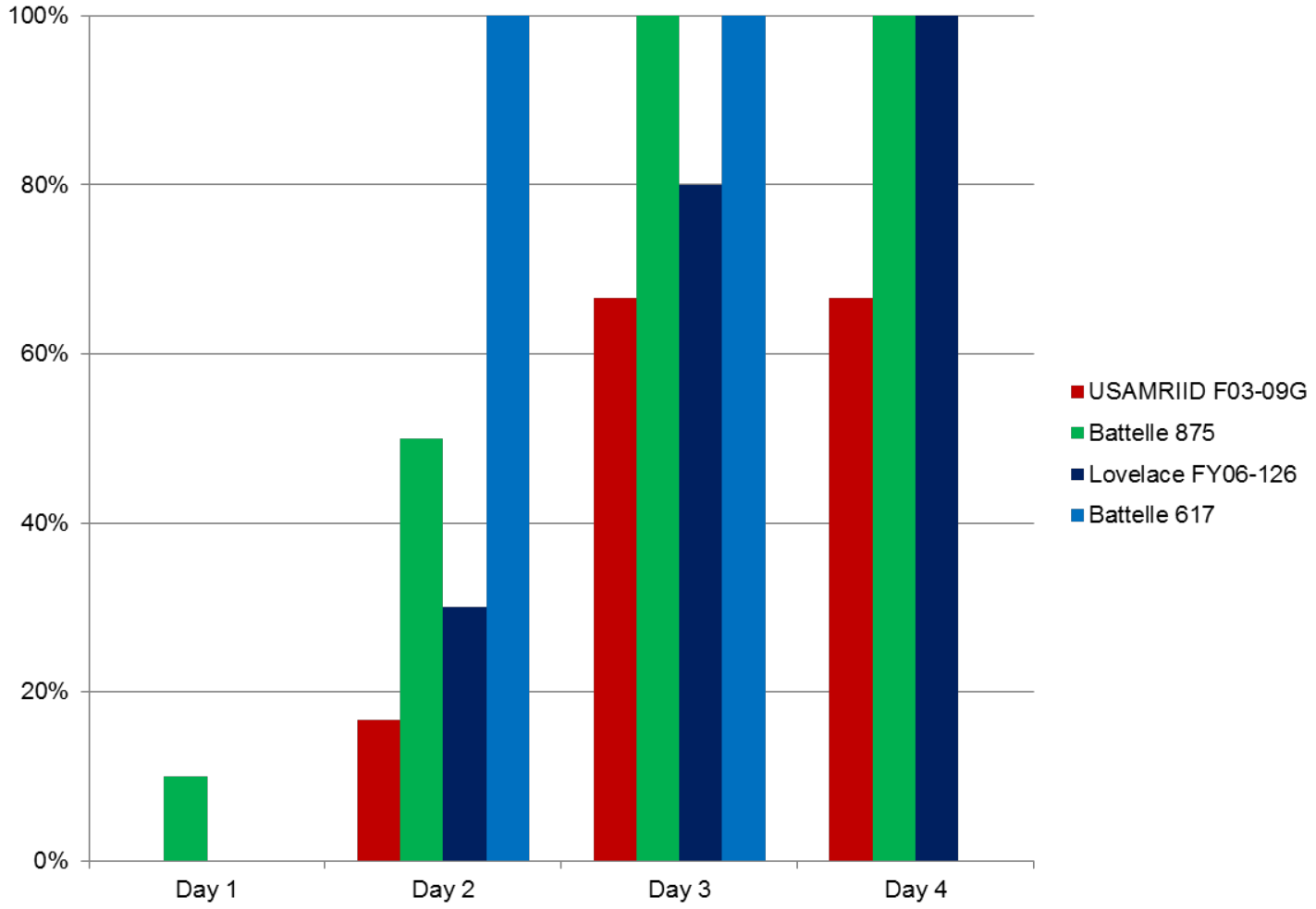
Bacteremia, across Studies



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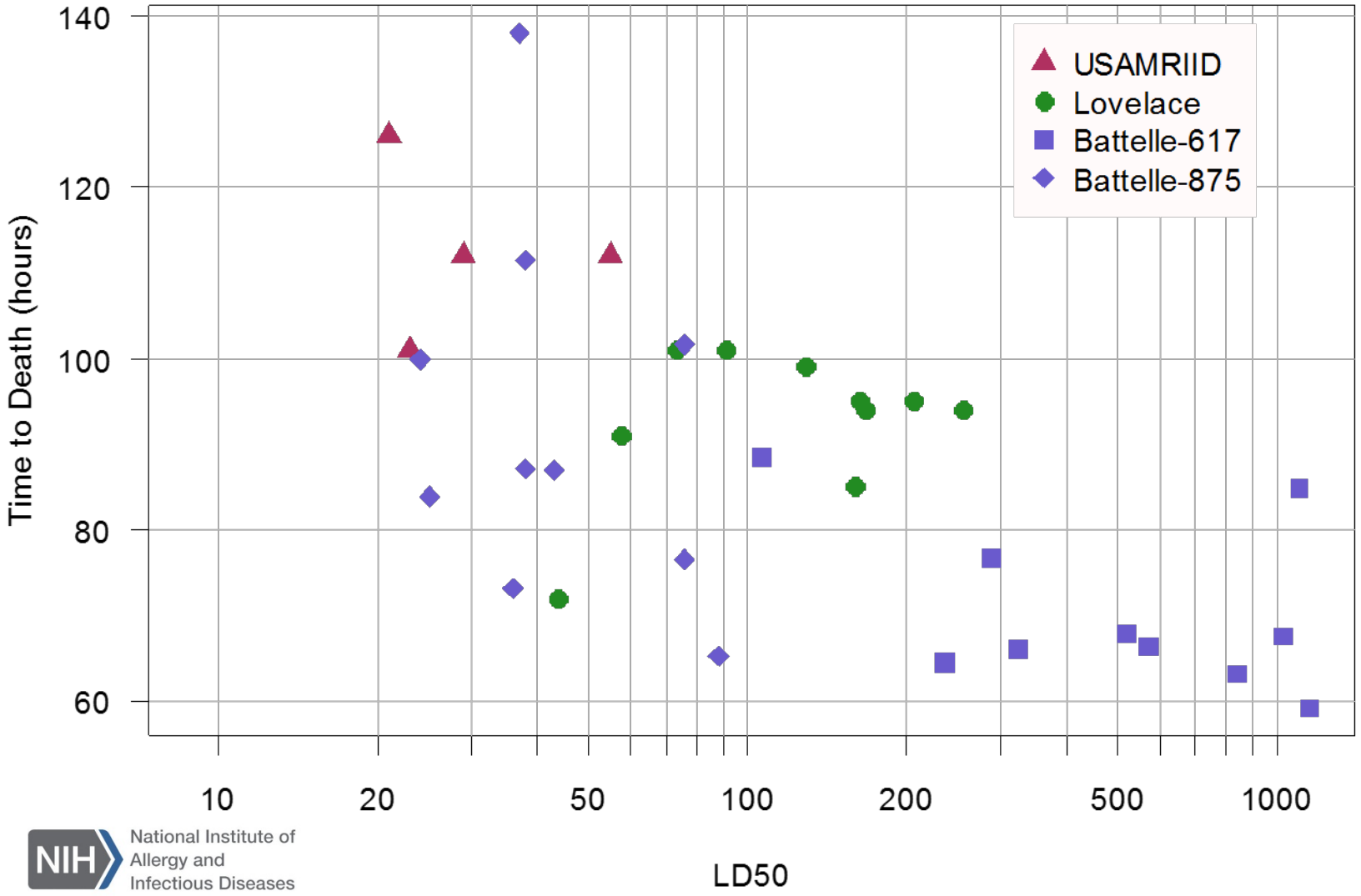
Time to Death by Challenge Dose



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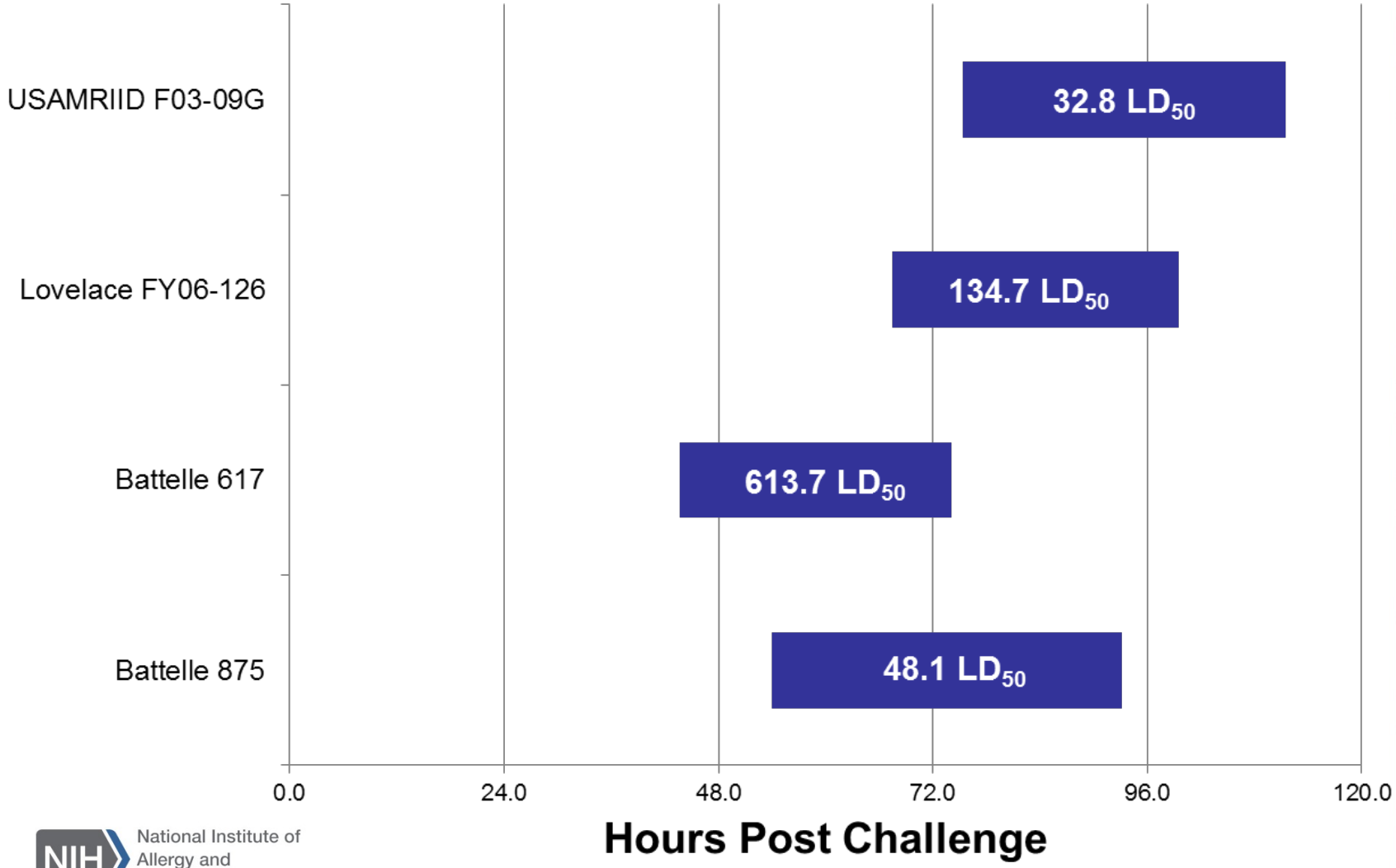
Mean Time from Fever to Death



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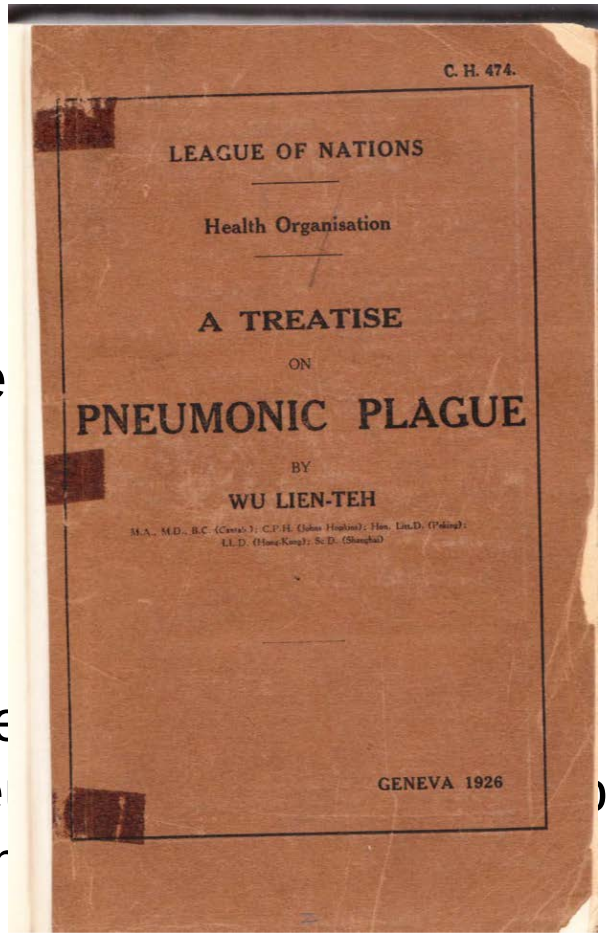
Lung Pathology – Incidence of Findings

# examined	F03-09G (4)	FY06-126 (10)	617 (10)	875 (10)	TOTAL (34)
Bacteria	4	9	10	10	33
Edema	3	6	10	10	29
Hemorrhage	4	10	8	9	31
Inflammatory infiltrate, intra-alveolar, macrophage	4	10	10	6	30
Inflammatory infiltrate, intra-alveolar, neutrophil	4	10	10	6	30
Necrosis, multifocal	0	0	0	4	4
Pleura, fibrin	3	10	3	8	24
Pleura, inflammatory infiltrate, macrophage	0	0	1	0	1
Within normal limits	0	0	0	0	0

Human Plague in the Modern Era

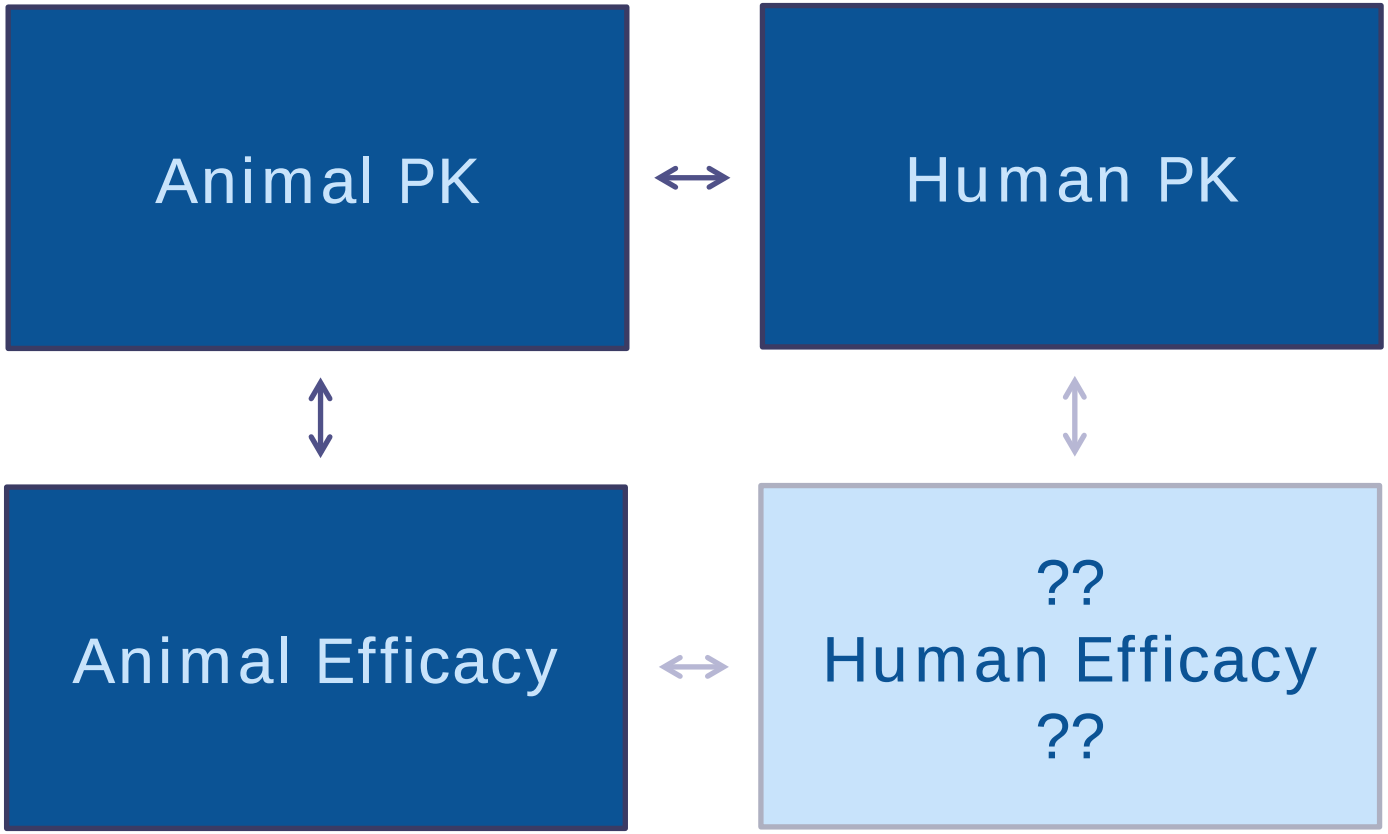
1855 – present
- China (1855)
- Russia (1877 – 1889)
- Hong Kong (1894)
  - Dr Yersin discovers bacterium
- Venice conference to keep Europe
- Hawaii (1899)
  - declared eradicated in 1959
- San Francisco (1900)
- Galveston (1920)
- Los Angeles (1924) 30 deaths (pne
- Surat, India (1994) 52 deaths (pne
- Congo (2006) ~100 deaths (pneum



Disease Comparison

Disease Feature	Human	AGM
Time course, days	2 to 9	2 to 9
Temperature	Elevated in 100% of cases	Elevated in 100% of cases
Y. pestis present	Positive in 100% of sputum	Positive in 100% of blood and/or lung/nasal fluid
Heart rate	Elevated	Elevated
Respiratory rate	Elevated	Elevated
Chest radiograph	Pulmonary infiltrates, 90% bilateral	Pulmonary infiltrates, 65% bilateral
Pathology, lung	Consolidations, Inflammatory infiltrates, Hemorrhagic/frothy fluid, Exudates and effusions, Bronchopneumonia, Bacilli	Bacteria, Edema, Hemorrhage, Inflammatory infiltrates, Bronchopneumonia, Pleural fibrin

Bridging from animals to humans



Lessons Learned

- Talk to FDA early about selection of animal model and correlation to human disease
- Standardize methods & reagents as early as possible
- Quality is extremely important
- Pharmacokinetics are extremely important
  - Establish SOPs
  - Use validated assays
  - Be careful with blood volumes and repeat assays
  - Draw blood samples from a different port/site than dosing
- Pivotal animal rule studies replace Phase III clinical trials for efficacy

Requirements of Animal Models for Animal Rule Studies

- Need to understand the human disease
  - Route of infection
- Develop animal model
  - Identify relevant strain, characterize, develop master & working bank
  - Select one or more species most relevant to humans
  - Collect data to identify relevant endpoints
  - Establish reproducibility of model
- Proof of concept for intervention (e.g., trigger to treat)
- Selection of an effective dose
- Quality systems to support efficacy testing of drugs (GLP, 21 CFR 58)

Generic GLP Challenge/Efficacy Study Timelines

Stage	Rodent	Rabbit	NHP
Animal Protocol Development	1 months	1 month	1-2 months
Animal Order, Receipt	2 weeks	0.5-1 month	2 months
Quarantine	1 week	1 week	1-1.5 months
Pre-study Surgery/Recovery		0-1 month	0-1 month
Pre-study Acclimation/Baseline	1 week	1 week	0.5-1 month
In-Life	1 month	1-2 months	1-2 months
Sample processing/Pathology	1-2 months	3-4 months	4-5 months
QC Data Review/QAU Auditing/Statistical Analysis	1 month	2-3 months	3-4 months
Draft Report	1 month	2-3 months	2-3 months
Final Report	0.5 month	1-2 months	1-2 months
TOTAL	6.5-7.5 months	11-17 months	15-24 months

Thank you!

"Enough with the low-hanging fruit. How about some slow-moving meat?"

BACKUP SLIDES

The Animal Efficacy Rule

FDA may grant marketing approval for a new drug product for which safety has been established and for which the requirements of 314.600 are met based on adequate and well-controlled animal studies when the results of those animal studies establish that the drug product is reasonably likely to produce clinical benefit in humans. In assessing the sufficiency of animal data, the agency may take into account other data, including human data, available to the agency. FDA will rely on the evidence from studies in animals to provide substantial evidence of the effectiveness of these products only when:

(1) There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;

(2) The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;

(3) The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and

(4) The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

21 CFR 314.600
21 CFR 601.90

The Need for the Animal Rule

- DoD desired drugs for biothreats against soldiers in Operation Desert Shield/Storm (1990-1) for anthrax, plague, chemical weapons
- USAMRIID studied ciprofloxacin, penicillin, doxycycline (+ vaccine) for anthrax prophylaxis in NHPs (Friedlander et al, JID 167:1239, 1993)
- Cipro was approved by FDA 8/30/2000
  - http://www.fda.gov/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/ucm130757.htm
  - Transcripts (7/28) http://www.fda.gov/ohrms/dockets/ac/cder00.htm#Anti-Infective
- Cipro approval used a surrogate endpoint under Subpart H, "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (21CFR314.500)
- FR notice for doxy & pen published 11/2/2001
  - http://www.fda.gov/OHRMS/DOCKETS/98fr/110201a.pdf

History of the Animal Rule

- 10/5/1999: FR notice proposing the Animal Rule
  - https://www.gpo.gov/fdsys/pkg/FR-1999-10-05/pdf/99-25377.pdf
  - Comment period closed 12/20/1999
- 5/31/2002: FR notice with Final Rule, becomes effective 7/1/2002.

- "On the Origin of the Animal Rule" (7/7/2010)
  - http://www.quintiles.com/library/experts/on-the-origin-of-the-animal-rule
- "FDA Experience with Medical Countermeasures under the Animal Rule" (7/21/2011)
  - https://www.hindawi.com/journals/apm/2012/507571/

Animal Rule Guidance Documents

- Final "Product Development Under the Animal Rule" Guidance issued October 2015.

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM399217.pdf

  - Public meeting held in November 2010
  - Draft Guidance issued in 2009, "Animal Models – Essential Elements to Address Efficacy Under the Animal Rule"

- Final "Qualification Process for Drug Development Tools" Guidance issued January 2014.

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM399217.pdf

  - Website published January 2012

    http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm

Animal Efficacy Rule Approvals to Date

Date	Drug	Indication
2003	Pyridostigmine Bromide	For military personnel exposed to Soman nerve gas
2006	Cyanokit (hydroxycobalamin) *	For cyanide poisoning
2012	Levaquin *	For treatment of pneumonic plague
	Raxibacumab	For treatment of inhalational anthrax, along with antibiotics
2013	*Botulism Antitoxin Heptavalent (Equine)*	For treatment of botulism
2015	Ciprofloxacin *	For treatment of pneumonic plague
	Anthrasil (anthrax immune globulin)	For treatment of inhalational anthrax, along with antibiotics
	Neupogen (filgrastim) *	For treatment of Hematopoietic Syndrome of Acute Radiation Syndrome
	Moxifloxacin *	For treatment of pneumonic plague
	Neulasta (pegfilgrastim) *	For treatment of myelosuppression after radiologic/nuclear incident
	BioThrax (vaccine)	For post-exposure prophylaxis of anthrax, with antibiotics
2016	*Obiltoxaximab (Anthim)*	For treatment of inhalational anthrax, along with antibiotics, and prophylaxis when alternative therapies are not available/appropriate.

* Drugs approved with a single animal model

italics = new drug

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No NIAID Involvement | NIAID Animal Model Used | NIAID Directly Involved

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4/3/2012 AdCom Discussion

1. Please comment on the similarities and differences between the African Green Monkey animal model of pneumonic plague and human disease with regard to:

a. Signs and symptoms

b. Outcome

c. Histopathology

2. Discuss the manifestations of pneumonic plague that could be used as a trigger for therapeutic intervention in the African Green Monkey animal model and their relevance to treatment of human disease.

4/2012 Drug Approval Discussions

- The AdCom votes for cipro and levo were unanimous for approval
- Discussed:
  - Small animal models
  - Recent human outbreaks
  - Other markers of disease
  - Statistics and power
  - A single animal model
  - Immediate treatment