FDA Perspective on Rabies mAb Clinical Trials Challenges

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Outline

- Review current PEP landscape
- Challenges in clinical trials
  - Role of serologic assays in rabies product evaluation
  - Trials conducted in healthy volunteers
  - Trials in suspected rabies virus-exposed populations
    - Superiority and Non-inferiority trials
- Safety
- Knowledge gaps

RIG as a Component of Rabies PEP

- **ACIP by Animal Type**
  - Skunks, raccoons, fox, bats regarded as rabid unless (-) testing
  - Dogs, cats, ferrets can be watched for 10 days if not suspected rabid
  - Livestock, rodents low risk
- **WHO by Exposure**
  - **Category II**: Nibbling of uncovered skin, minor scratches or abrasions (without bleeding). *PEP recommendation does not include RIG.*
  - **Category III**: Single/multiple transdermal bites or scratches, licks on broken skin; contamination of mucous membranes with saliva (licks); contacts with bats
- **Regimen (if have not received prior PrEP)**:
  - Begin as soon as possible, though no time limitation for initiation

	ACIP	WHO Category III Exposures
Extensive wound cleansing	Day 0	Day 0
RIG^	HRIG Day 0*	HRIG or ERIG Day 0*
Rabies vaccine	IM Day 0, 3, 7, 14	IM Day 0, 3, 7, 14, 28 or Day 0, 7, 21 ID Day 0, 3, 7, 28 (Thai Red Cross schedule)

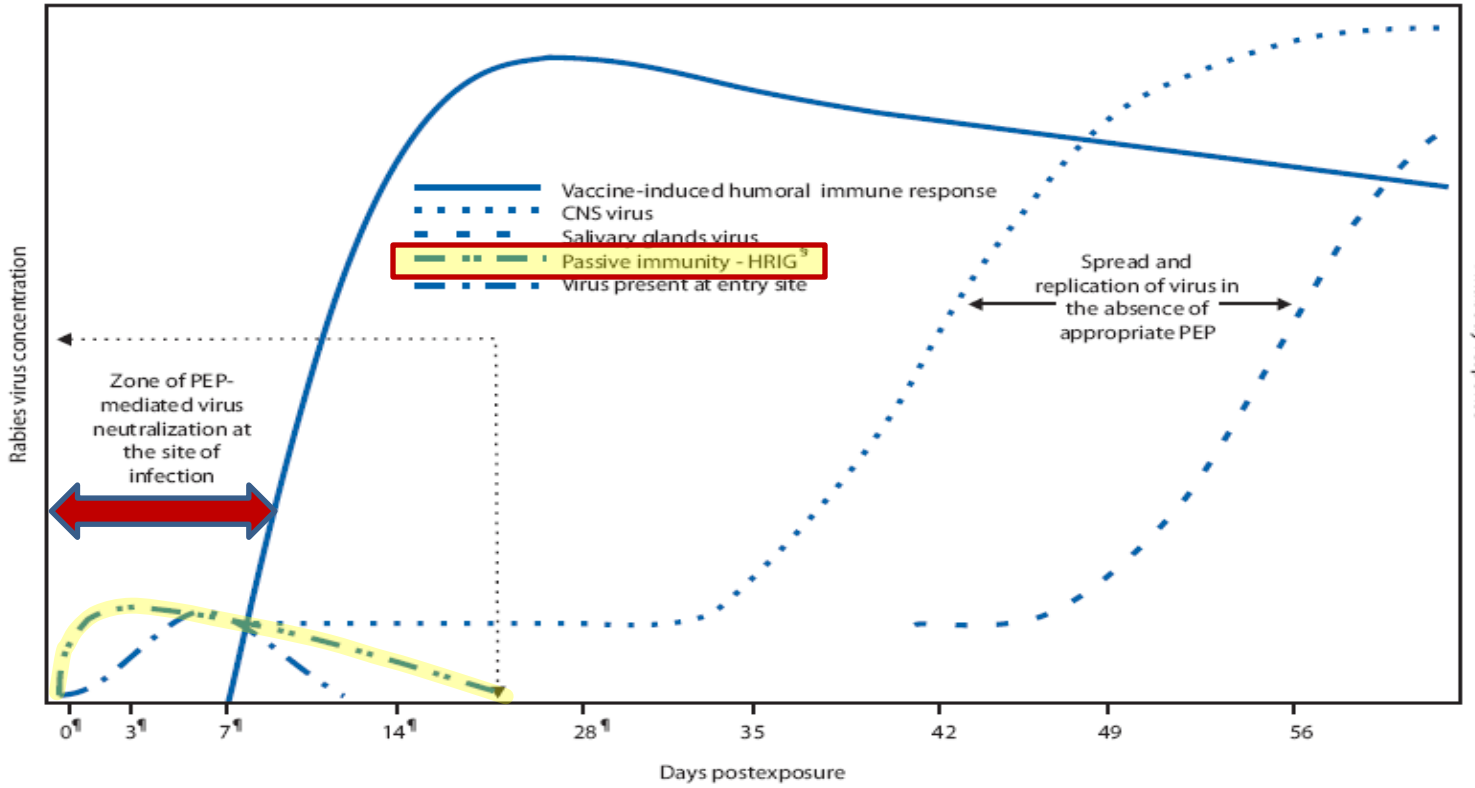
^As much as anatomically feasible should be infiltrated in area around/in wound: any remaining dose IM
*Do not administer RIG after Day 7 of rabies vaccine (in cases where delayed RIG)

PEP Failures

- Most commonly hypothesized explanations:
  - RIG not used at all, injected only IM and not into wounds, or not all bite wounds injected
  - Vaccine or RIG is of low potency
  - An exceptionally large Rabies viral load was introduced.
  - Atypical virus that is not neutralized by RIG or by natural antibodies resulting from vaccination
  - Inadequate wound care
- PEP courses without RIG may be fairly frequent; unclear what proportion of these fail

Contribution of Passive Immunization to PEP Regimen

FIGURE 1. Schematic of dynamics of rabies virus pathogenesis* in the presence and absence of postexposure prophylaxis (PEP)–mediated immune responses†



* Rabies can progress through five stages: incubation period (5 days to >2 years: U.S. median ~35 days), prodrome state (0–10 days), acute neurologic period (2–7 days), coma (5–14 days), and death.

† Once in tissues at the entry site, rabies virus can be neutralized by passively administered rabies immune globulin (RIG). Active immunization (vaccine) stimulates the host immune system, and, as a result, virus-neutralizing antibodies (VNA) are produced approximately 7–10 days after initiation of vaccination. By approximately day 14–28 (after administration of 4 vaccine doses), VNAs peak. In the absence of early and adequate PEP, virus enters host neurons, spreads to the central nervous system (CNS), and causes disease, with inevitably fatal consequence.

§ Human rabies immune globulin.

¶ Day vaccine administered.

Adapted from *CDC. Use of a Reduced (4-Dose) Vaccine Schedule for Postexposure Prophylaxis to Prevent Human Rabies: Recommendations of the Advisory Committee on Immunization Practices. MMWR 2010;59(No. RR-2).*

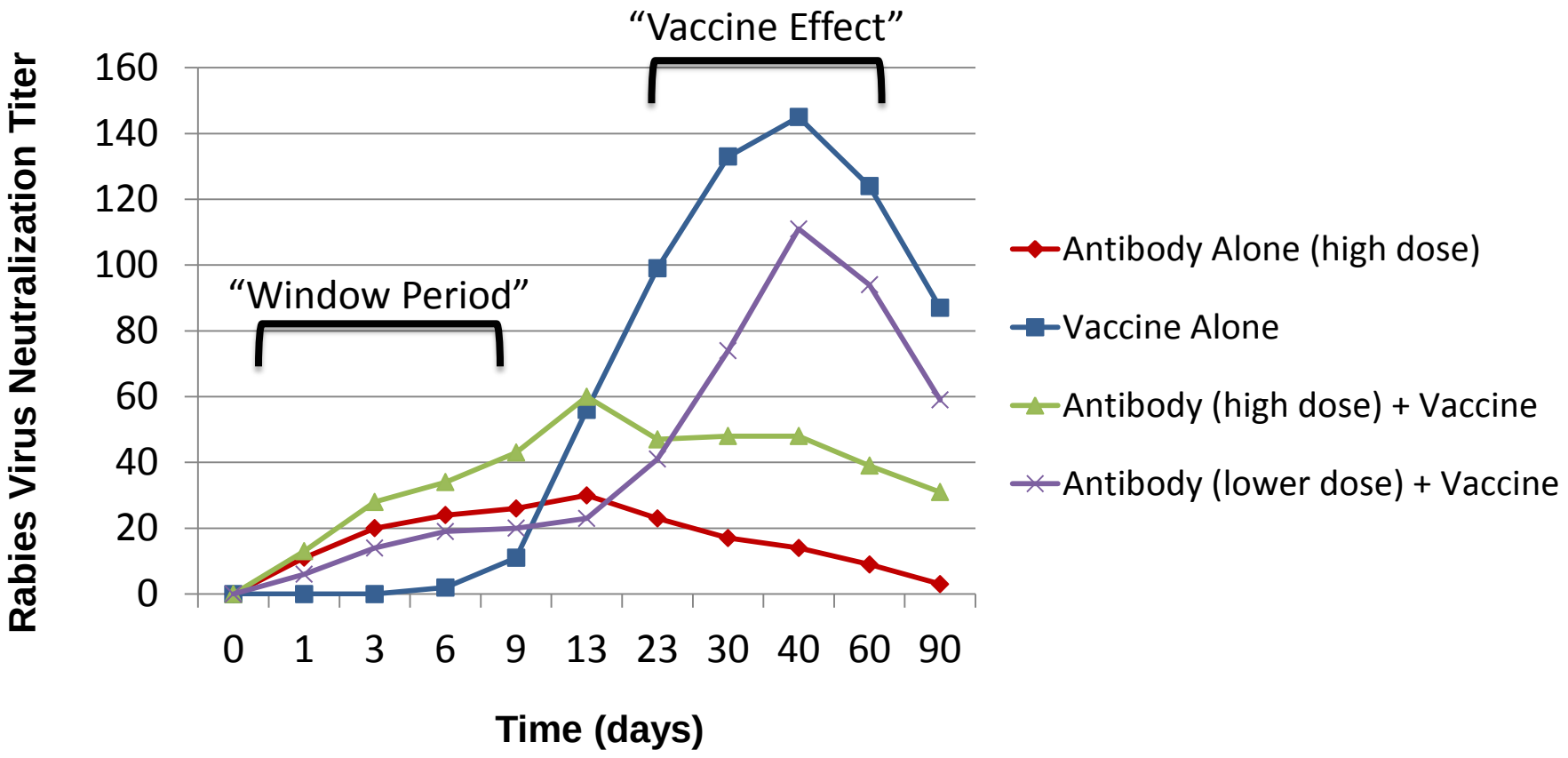
Serologic Assays

Example: Rabies Virus Neutralizing Abs (RVNA)

- Rapid fluorescent focus inhibition test (RFFIT)
  - Acceptable antibody response to rabies virus: complete neutralization of challenge rabies virus for **vaccine**
    - ACIP: serum dilution of 1:5 using RFFIT, (0.1 IU/mL)
    - WHO: uses higher cutoff of ≥ 0.5 IU/mL
  - No established RVNA threshold for passive immunization
  - RVNA level after vaccine may be accompanied by other aspects of vaccine response (including cell mediated immunity and capacity for an anamnestic response)

Dynamics of Rabies Virus Neutralizing Antibodies Levels in Context of Passive Antibody Product +/- Vaccine

Hypothetical Example



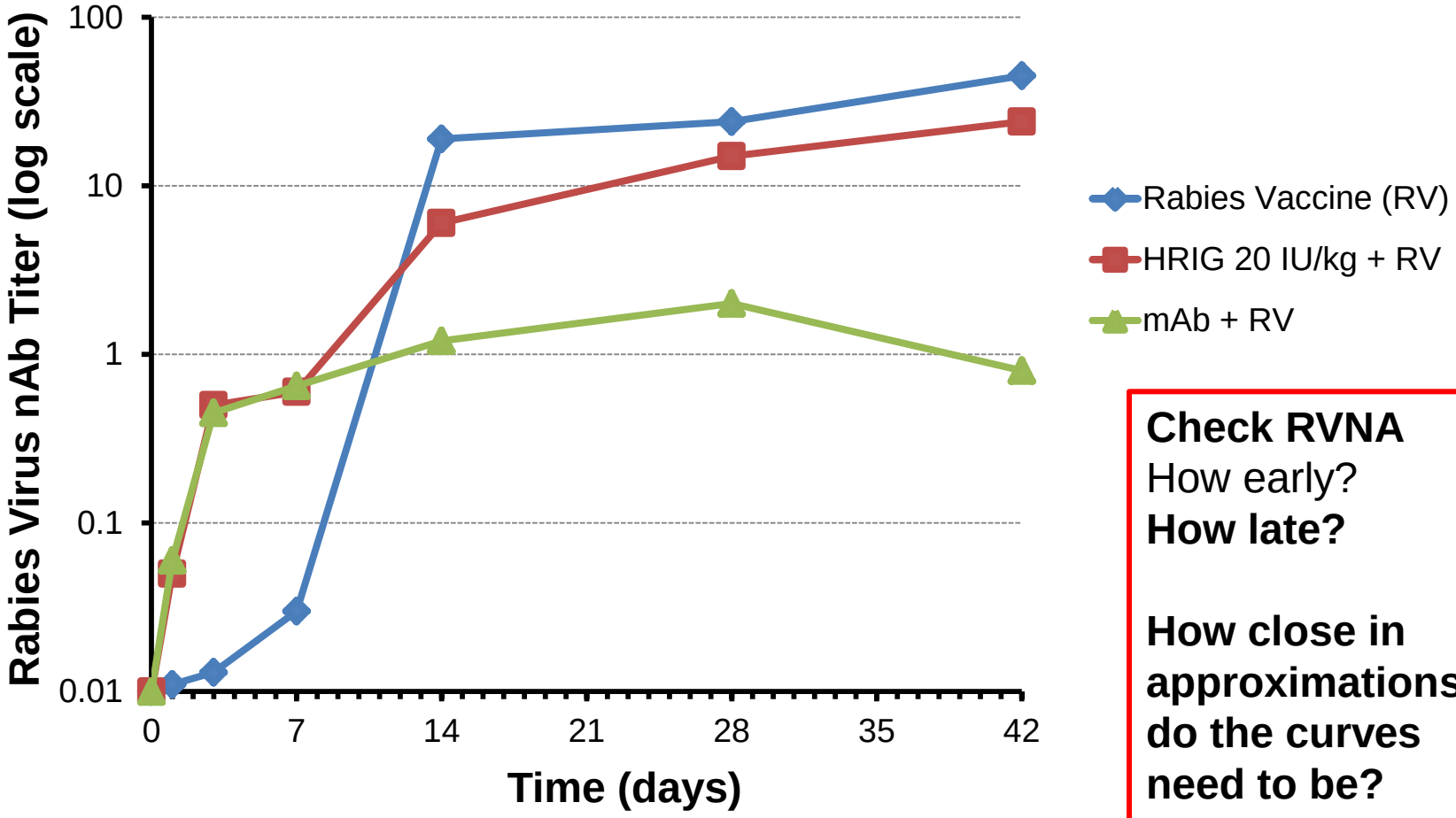
Challenges with Interpretation of Serologic Assay Data

- What level is needed during the first few days to provide protection?
- At what time points should serologic assays be measured?
- Can assays results for mAb and HRIG be compared and what level of comparability is sufficient?
- What do serum measurements tell you about protection at wound site? Is there any other way to assess protection at wound site in the clinical setting?

Clinical Trials with Rabies mAb
Non-Rabies-Exposed Population

- Study of different components (and combined regimens) of established and proposed PEP in non-rabies-exposed healthy volunteers
- Initial exploration of tolerability and adverse event profile
- mAb dose exploration
  - Can higher doses be identified as excessively interfering with active response to vaccine?
  - Can lower doses be identified as unlikely to provide adequate protection during the earliest time period before protective vaccine response begins to be established?
- What serologic assay parameters (levels and timing) are most predictive of protection after rabies exposure?

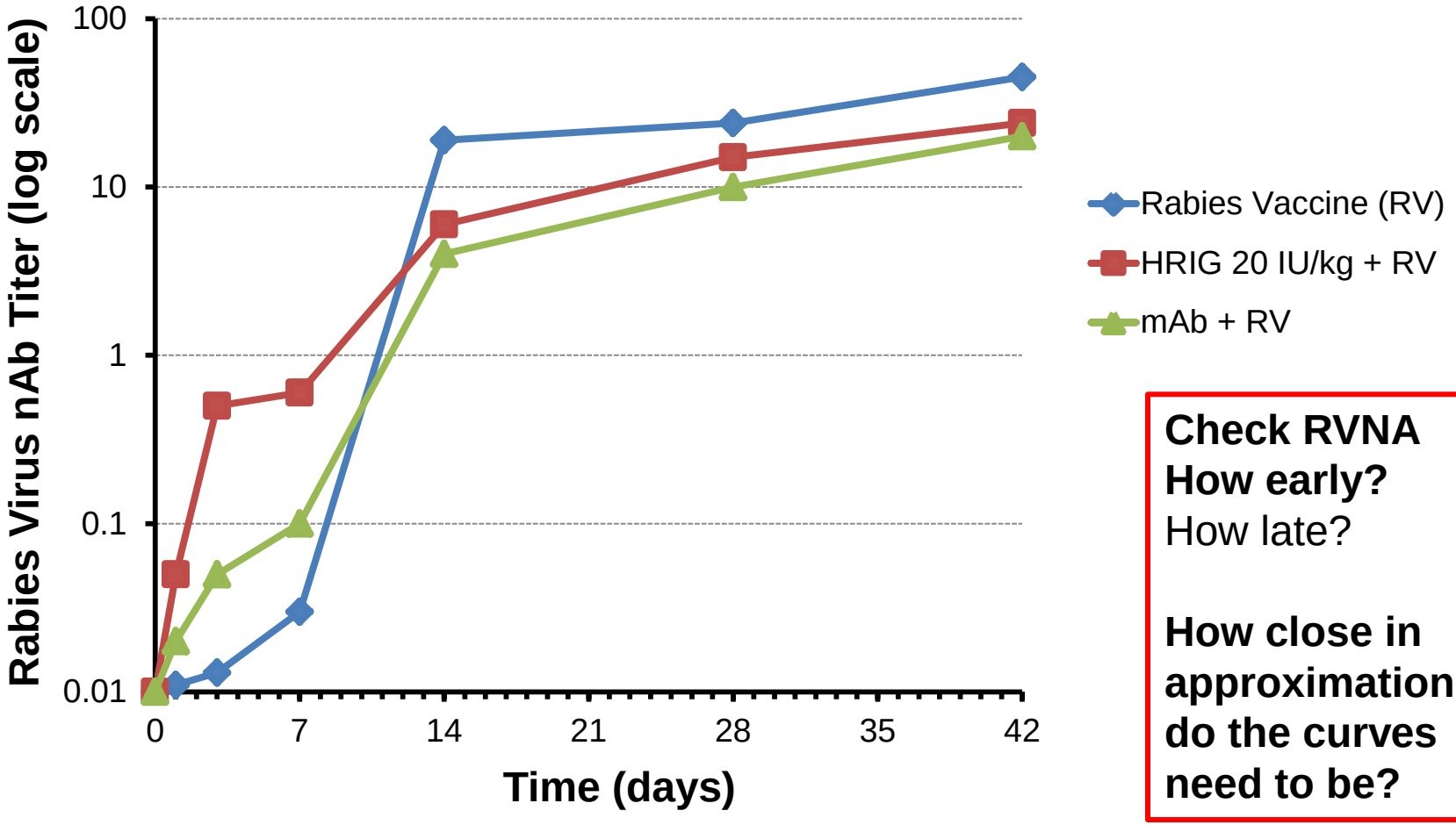
Interpretation of RVNA data
Hypothetical mAb vs. HRIG: Scenario 1



Check RVNA
How early?
How late?

How close in approximations do the curves need to be?

Interpretation of RVNA data
Hypothetical mAb vs. HRIG: Scenario 2



Check RVNA
How early?
How late?

How close in approximations do the curves need to be?

Challenges in Applying RVNA Data to Clinical Wound Scenarios

- How much do serologic measurements after IM injection tell us about neutralizing activity after local infiltration at a bite site?
  - But on the other hand, is there a better way of measuring what is happening at the bite site in the clinical setting?
  - What about complex wounds, multiple wounds, or occasions where no wound is visible (bat exposure)?

Totality of Data to Support Evaluation of a Rabies mAb in a Rabies Exposed Population

- What data are needed to support study of a mAb as part of PEP to patients with suspected rabies exposure?
  - Avoiding unnecessary risk to patient is both an ethical and safety issue
  - Choice of dose is critical for beginning trials in rabies exposed patients because the outcome of a PEP failure is death

Clinical Trials with Rabies mAb

Suspected Rabies-Exposed Population

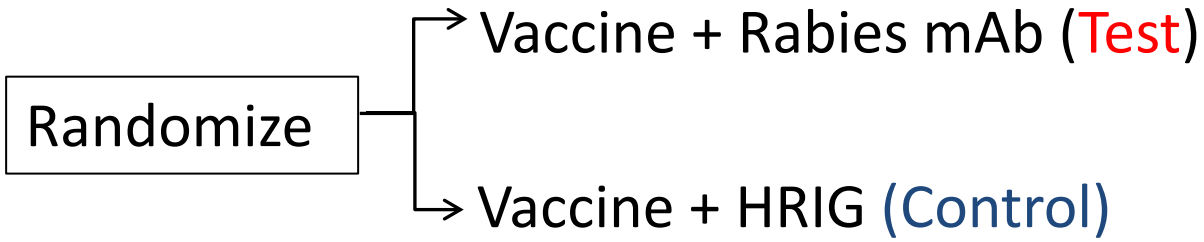
- Adequate regulatory evidence for approval
- Informed public health and clinical decision-making
- Many challenges in designing and interpreting clinical trials of a proposed novel component of rabies PEP
- Clinical importance of an active control comparison (mAb +rabies vaccine vs. RIG +rabies vaccine)
  - Highly effective approved regimen
  - Outcome of PEP failure is mortality

Trial Design Considerations

- Clinical trials are generally designed to demonstrate either superiority or non-inferiority.
  - Superiority objective: to demonstrate the new product is superior to the control.
  - NI objective: to demonstrate that the new product is not unacceptably worse than the control, based on a pre-specified NI margin (M).
- Objective in clinical trials in the suspected rabies-exposed population is to decrease the risk of developing fatal rabies infection

Superiority Trial (1)

Example-1:
Hypothesize that the following trial could be designed to demonstrate superiority of Rabies mAb to HRIG.



Benefits:

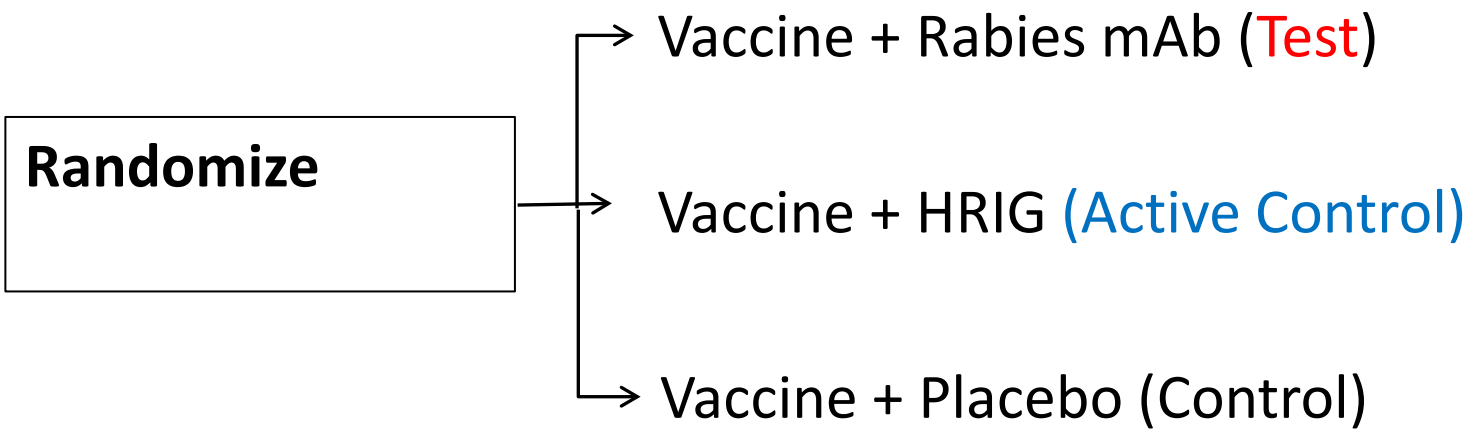
- **Provides direct evidence of treatment benefit**
- **Easily interpretable if there is a clear difference in the treatment arms**

Challenges:

- **The success rate for the Vaccine + HRIG could be close to ~100%; therefore, the ability to demonstrate superiority could be difficult**
- **Large sample size required**

Superiority Trial (2)

Example-2:
Hypothesize Vaccine + Placebo group can be included in a 3-arm trial design.



Benefits:

- **Provides direct evidence of treatment benefit if it shows superiority to placebo along with internal consistency (HRIG)**
- **Easily interpretable**

Challenges:

- **May still be difficult to show superiority depending on the population and the efficacy of vaccine alone**
- **Ethical concerns are important**

Superiority Trial: Sample Size

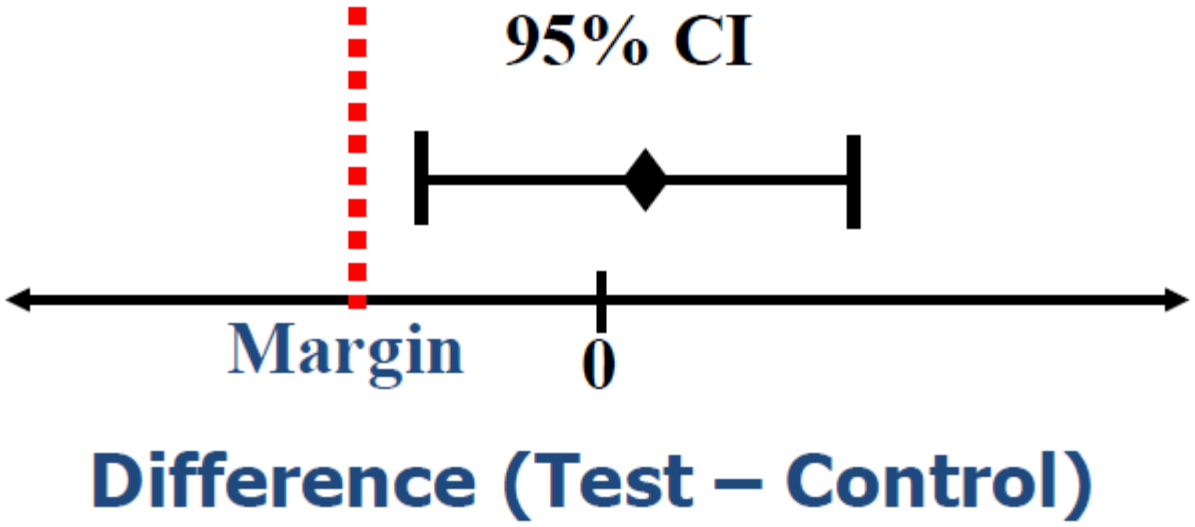
Survival Outcome

Control	Test	Treatment difference	Sample Size per Group
98%	99%	1%	2500
97%	99%	2%	830
96%	99%	3%	450
95%	99%	4%	305

Method: Fisher's Exact; α=.05 2-sided, power 80%

Non-Inferiority (NI) Trial

Objective: To demonstrate that the efficacy of **Test** is **not unacceptably worse** than the **Active Control**, based on a pre-specified NI margin.



NI Trials: Key Concepts (1)

- **Assay Sensitivity:** Ability of the NI trial to distinguish an effective investigational product from an ineffective product

- **Constancy of Treatment Effect**: Constancy of the efficacy of an active control in the current NI trial compared to historical evidence

- **Assessment of the quality of the NI trial**

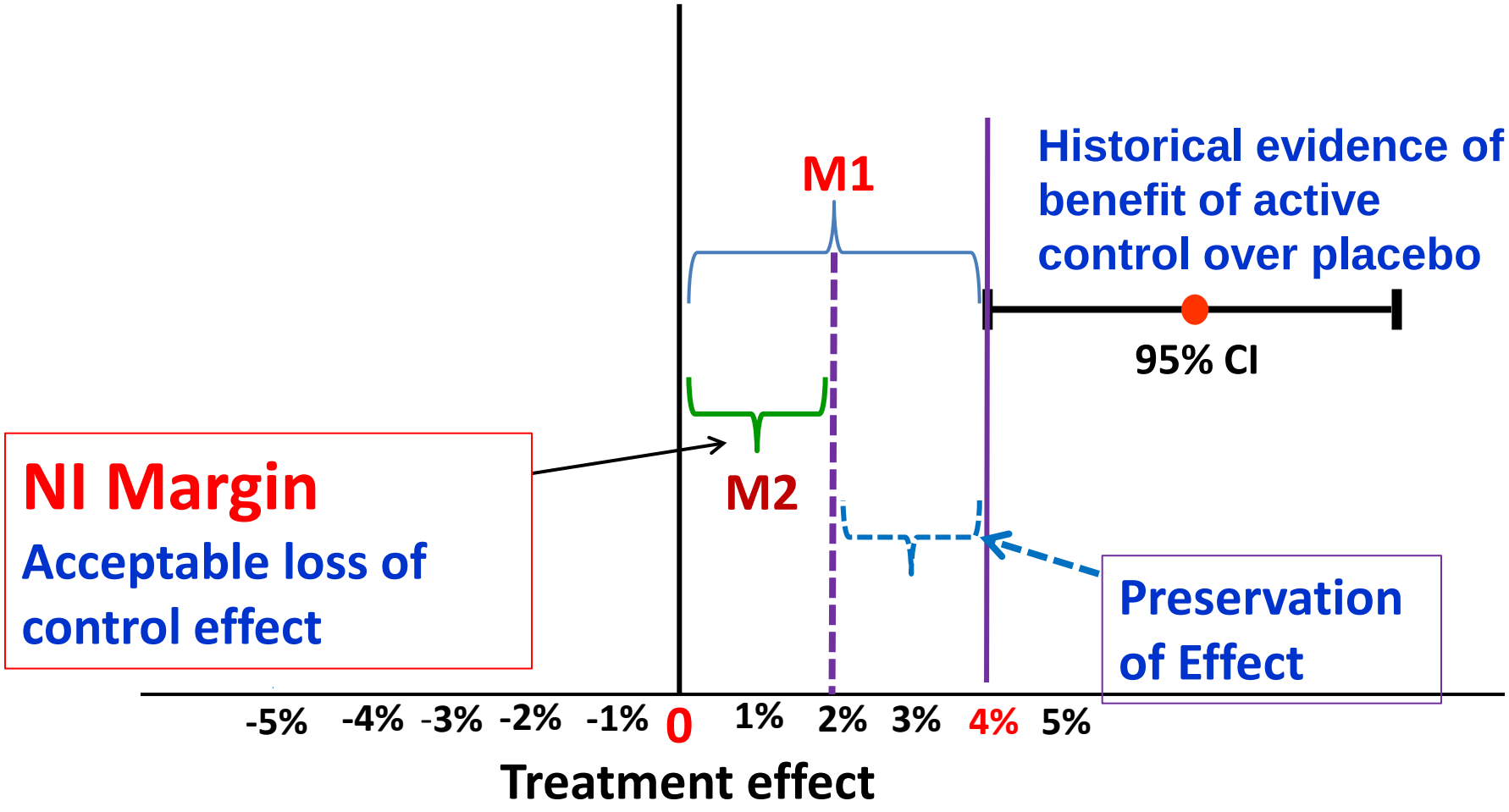
  Quality of the NI trial is not compromised making the findings uninterpretable

NI Trials: Key Concepts (2)

- **M1 (Active control effect over placebo)**
  - Based on historical evidence of treatment benefit
  - May be adjusted to account for heterogeneity

- **M2 (NI Margin); M2 < M1**
  - Clinically acceptable loss of efficacy for the test product compared to active control

Determination of NI Margin



NI Trial Design

- **Benefits:**
  - Potential pathway to assess effectiveness if a superiority trial is infeasible

- **Challenges:**
  - Choice and justification of the NI margin
  - Sample Size
  - Specific to clinical trials in suspected rabies-exposed population:
    - Interpretation of the findings may be challenging if the contribution of HRIG added to vaccine is unknown or unreliable for the mortality endpoint.

Rabies Serum Experience, Trial Using Antiserum in an Iranian Wolf

- **N=18 Severe Head wounds**
  - 7 Serum (1 serum injection) + Vaccine -> 1/7 deaths
  - 6 Serum (≥ 2 serum injections) + Vaccine -> No deaths
  - 5 Vaccine -> 3/5 deaths
- **N=11 Limb/Trunk wounds (divided into 2 series)**
  - Serum+Vaccine (4) or Vaccine alone (7) -> No deaths

Decreased mortality rate of 8% (1/13) among persons with head wounds treated with Serum+Vaccine compared with 60% (3/5) mortality treated with Vaccine alone

Note: serum is rabbit serum globulin and vaccine is sheep brain derived vaccine

Baltazard M. Bull. Wld Hlth Org. 1955, 13, 747-772

Challenges with Establishing an NI Margin

- Limitations in generalizing the treatment difference observed in this trial includes
  - Small sample size
  - Unusually severe attack scenario
  - Different vaccine (sheep brain derived)
  - Different passive antibody (rabbit antiserum)
  - Different route of administration
- NI margin assumes constancy of the treatment effect which is not apparent from these data

Alternative Trial Design Considerations

- Are there other trial design considerations in suspected rabies-exposed population that may be feasible, ethical, and interpretable?
  - Dose response
    - At least same issues as a superiority trial
  - Historical control
    - At least same issues as a non-inferiority trial
- Other ideas for discussion

Alternative Endpoints?

- In what ways can serologic assays be informative in trials in the suspected rabies-exposed population?
  - What time points are informative? If measurement times differ from healthy-volunteer studies, why?
- Are there other measurements that may be informative?
- What duration of follow up is needed to establish clinical relevance?

Other Trial Considerations

- Geographical differences in rabies animal vectors, virus strains, and PEP regimens
  - Interpretability and generalizability across different populations at risk
- Trial site capability
  - Confirmation of the rabies status of the animal, serologic testing, patient follow-up
- Inclusion criteria considerations
  - "Low risk" WHO Category III exposures initially (e.g., limb wounds), followed by higher risk exposures?
    - Can results be informative in a "low risk" population who may be expected to have high survival with adequate wound care and rabies vaccine alone?
  - Enrichment with population experiencing more severe head wounds?
  - Timing of enrollment after bite?

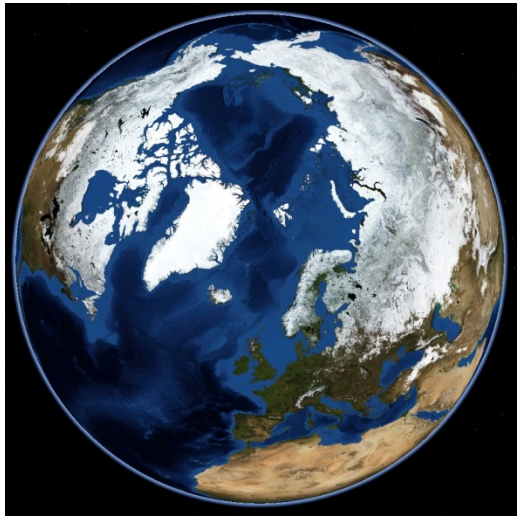
Potential Safety Concerns with mAbs

- Experience with mAbs in general have shown side effects such as allergic type reaction, flu like symptoms, gastrointestinal symptoms, hypotension
  - Full safety spectrum of novel mAb not yet defined
- Similar reactions can occur with plasma derived products
- Efficacy issues are also safety concerns
  - Vaccine interference
  - Narrower spectrum of rabies virus coverage

Potential Knowledge Gaps

- Contribution of passive antibody to PEP regimen may be difficult to ascertain.
- Case reports of PEP failure do not provide information on what proportion of persons receiving current PEP lacking only RIG component develop rabies.
- Regarding clinical trials, what types of clinical trials may be interpretable, feasible, and ethical?
- How can indirect measurements such as serologic assays apply to trials in the suspected rabies-exposed population?
  - How can serologic assays help determine if people with rabies exposure are being protected from a fatal disease?
- What neutralization happens at the bite site and how can this be measured?

Looking Forward to These and Other Discussion Points



Thank you

BACK UP/Extra slides

Example of Enrichment
Case series from 1950s Iran

- N=325 with wolf bites: All received rabies vaccine (rabbit or sheep-brain derived)
  - 18.5% died (N=60)
- By bite site:
  - Head wounds (N=186), 28% developed rabies
  - Arm wounds (N=74), 9% developed rabies
  - Trunk/leg wounds (N=65), no development of rabies
- If consider only those where rabies in biting animal proven by death of 1+ bitten:
  - Overall ~25% developed rabies
  - Head wounds, 42% developed rabies

Baltazard M. Rev. Immunol. (Paris), 1953, 17, 366