

Opportunities and Challenges for Development of Monoclonal Antibodies for Use in Rabies Post-Exposure Prophylaxis

FDA Public Workshop
Sarah Connelly, MD
Senior Medical Officer, Division of Antiviral Products
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Today's Public Workshop

Objective: Discuss the challenges and identify additional scientific work needed to advance development of monoclonal antibodies (mAb) targeting rabies virus for use in a post-exposure prophylaxis (PEP) regimen, to be used in conjunction with licensed rabies vaccine.

 **Public workshop** to facilitate sharing of the available data and complexities in the field of rabies PEP

– Note: Not an advisory committee, decisional meeting, or regulatory meeting on any specific product or products

 Forum for discussion and for identifying research gaps relevant to regulatory and public health issues

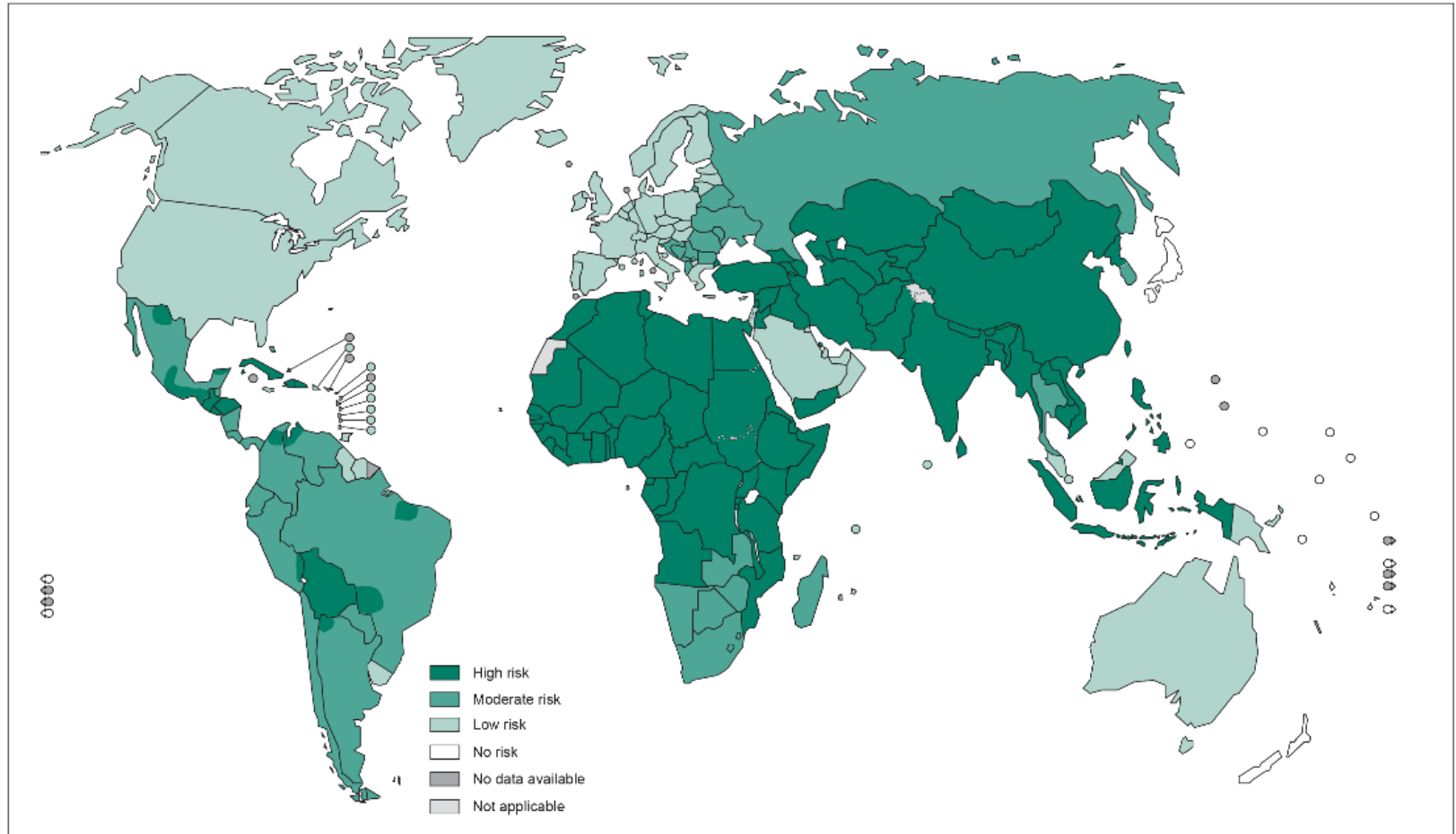


Rabies Background

- **Fatal encephalitis** of mammals resulting from rabies virus infection
- **No established current treatment**; survival is rare
 - ~55,000 deaths/year worldwide (95% Asia, Africa, Latin America)
- **Prevention**
 - **Animal vaccination**
 - **Pre-exposure prophylaxis (PrEP)**
 - Rabies vaccine
 - **Post-exposure prophylaxis (PEP)***
 - Rabies vaccine plus immunoglobulin (*if prior PrEP, only vaccine)
 - ~11,000-36,000 persons/year receive PEP in the US
 - 15+ million persons/year receive PEP worldwide

Global Risk of Rabies

Distribution of risk levels for humans contacting rabies, worldwide, 2013



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2014. All rights reserved

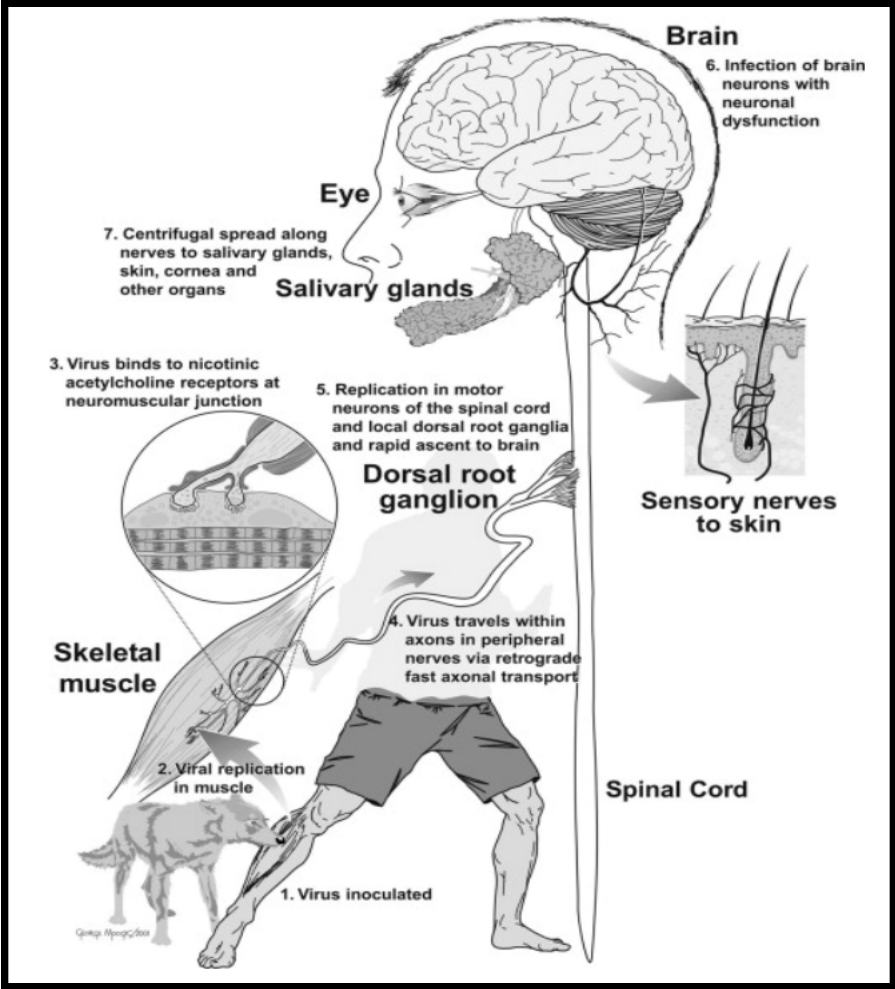
Data Source: World Health Organization
 Map Production: Control of Neglected Tropical Diseases (NTD)
 World Health Organization



Rabies Virus Vectors



Rabies Pathogenesis After Animal Exposure

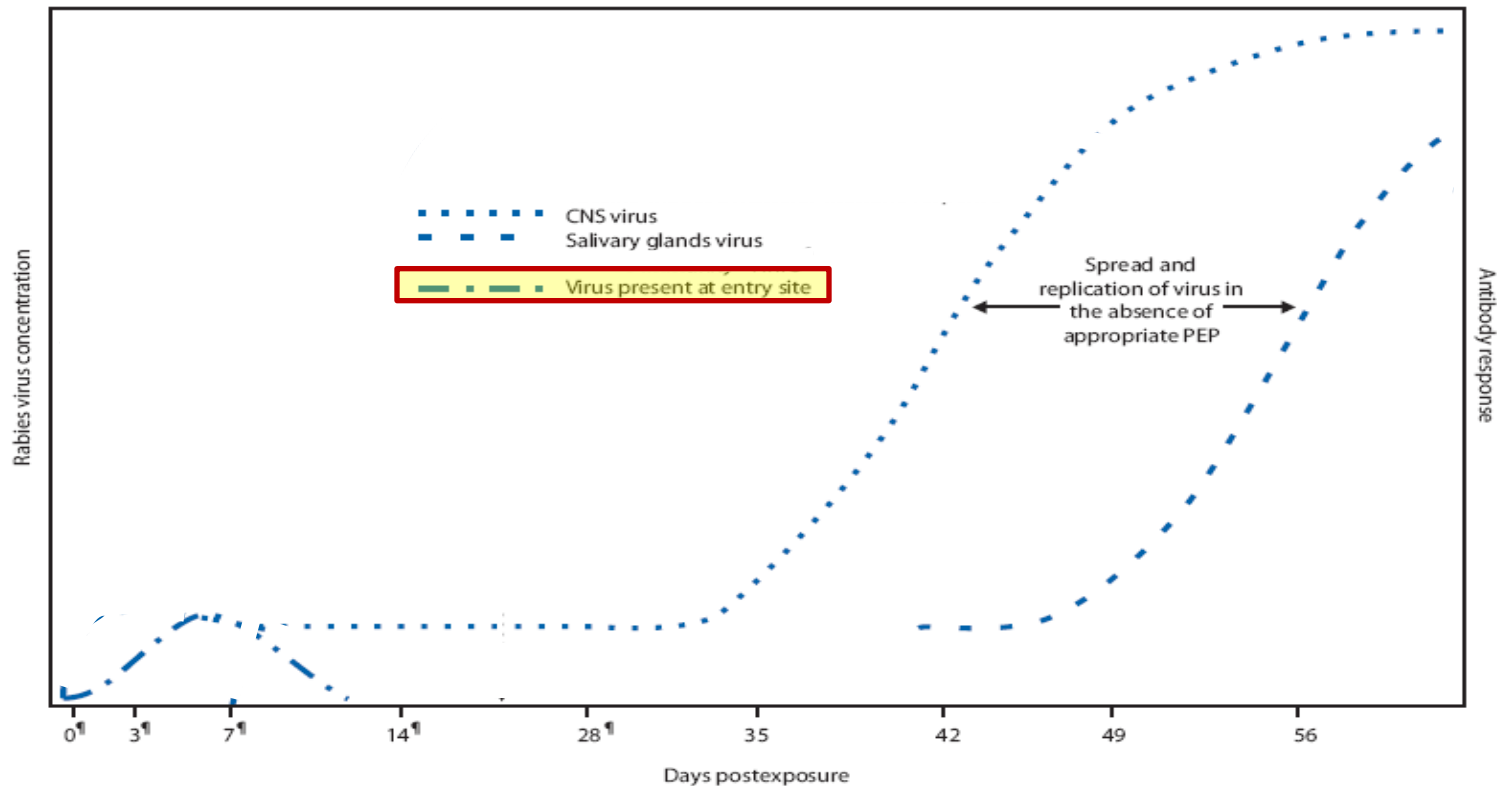


Jackson, A.C., 2007. Pathogenesis. In: Jackson, A.C., Wunner, W.H. (Eds.), Rabies, second ed. Elsevier Academic Press, London, pp. 341–381

Dynamics of Rabies Virus Pathogenesis



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



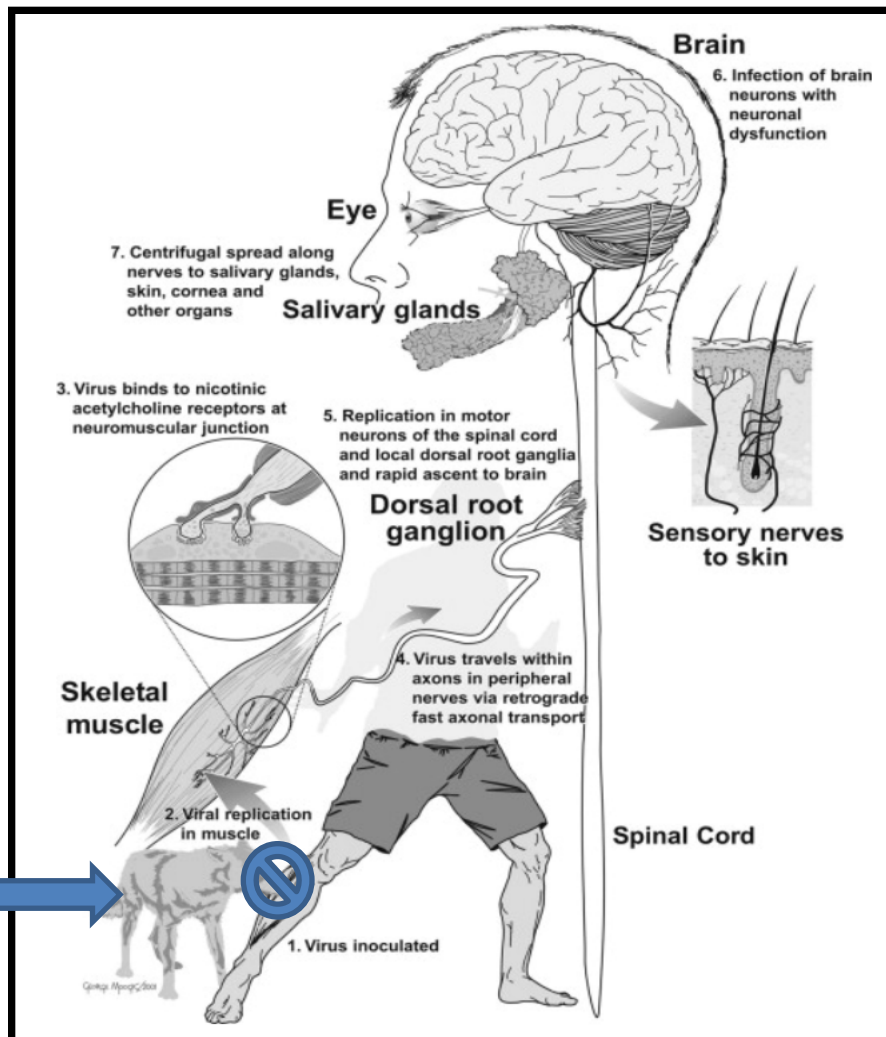
* Rabies can progress through five stages: incubation period (5 days to >2 years: U.S. median ~35 days), prodrome state (0–10 days), acute neurologic period (2–7 days), coma (5–14 days), and death.

† 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.

Role of PEP After Animal Exposure



Role of PEP

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)

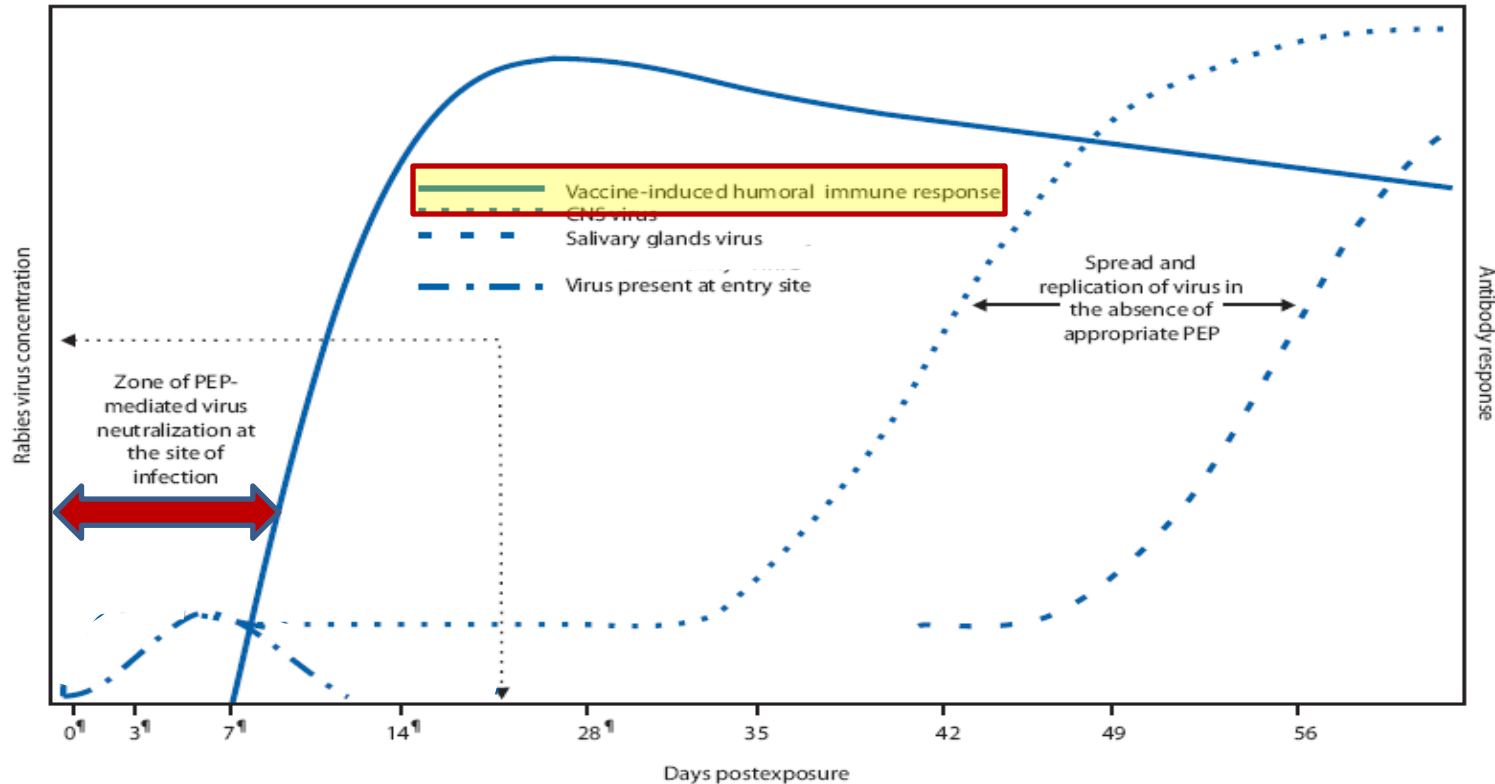
[^]As much as anatomically feasible should be infiltrated in area around/in wound: any remaining dose IM

*Do not administer RIG after Day 7 of rabies vaccine (in cases where delayed RIG)

Rabies Vaccine-Mediated Immune Response



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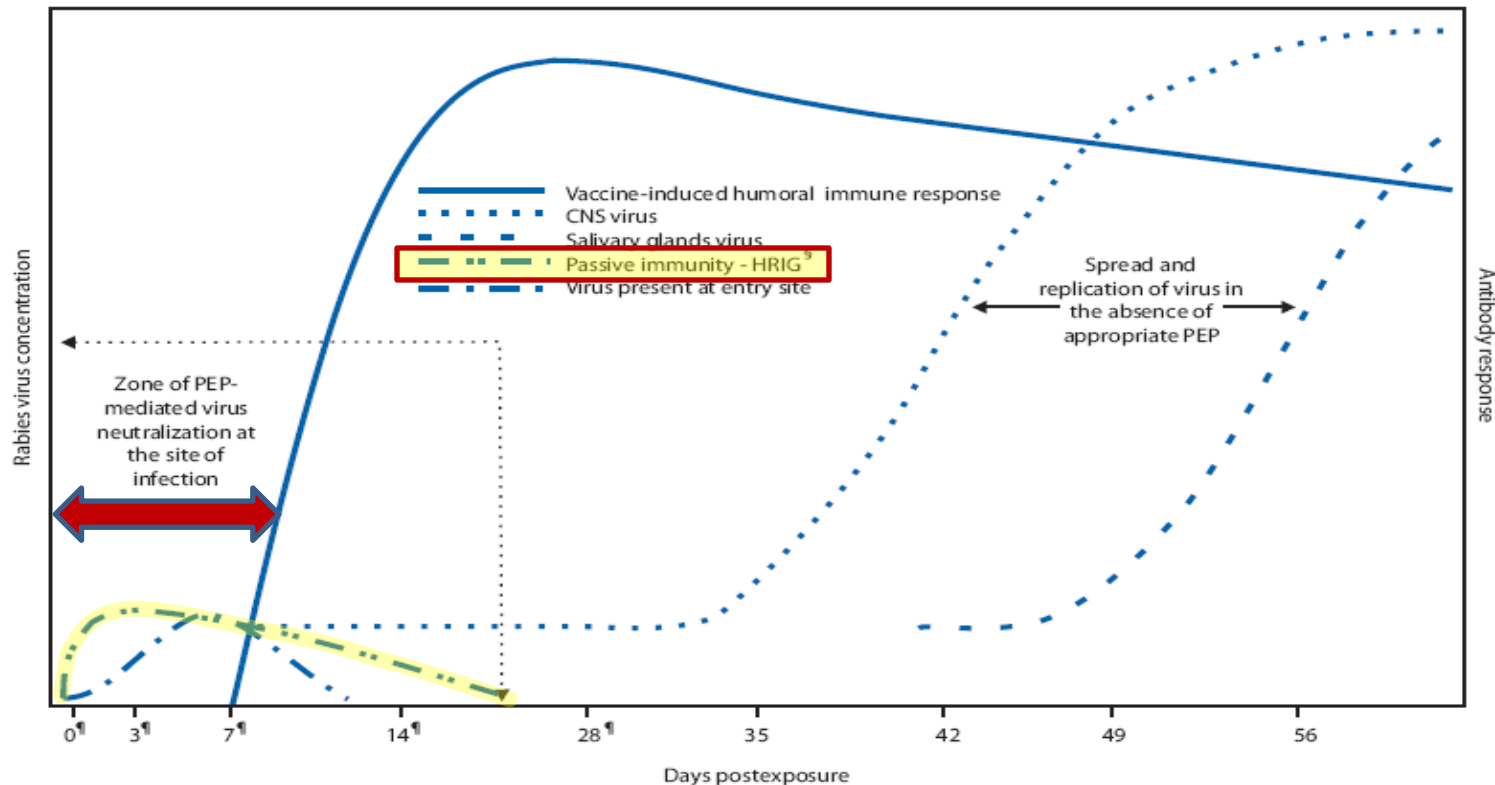
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Contribution of Passive Immunization to PEP Regimen



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Rabies Immunoglobulin



US approved Human RIG Products

HyperRAB S/D

The usefulness of prophylactic rabies antibody in preventing rabies in humans when administered immediately after exposure was dramatically demonstrated in a group of persons bitten by a rabid wolf in Iran. Similarly, beneficial results were later reported from the U.S.S.R. Studies coordinated by WHO (World Health Organization) helped determine the optimal conditions under which antirabies serum of equine origin and rabies vaccine can be used in man. These studies showed that serum can interfere to a variable extent with the active immunity induced by the vaccine, but could be minimized by booster doses of vaccine after the end of the usual dosage series.

Imogam

Controlled human trials of Rabies Immune Globulin (Human) have not been performed; however, extensive field experience from many areas of the world indicates that post-exposure prophylaxis combining local wound treatment, local infiltration of rabies immune globulin (RIG), and vaccination is uniformly effective when appropriately administered.

Perspective on Use of Current PEP Regimens



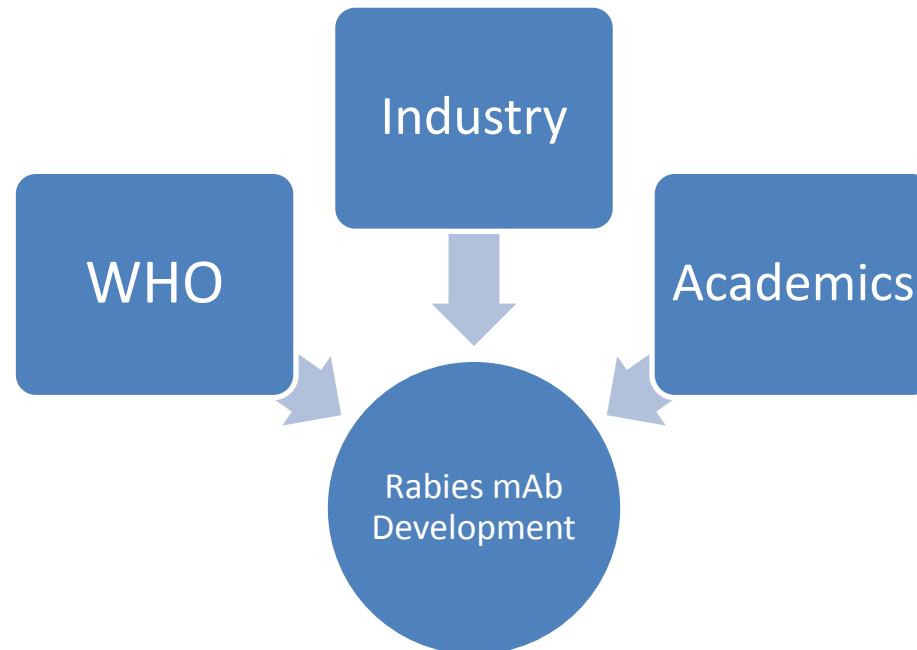
- Available approved/licensed rabies vaccine and RIG products are considered highly effective at preventing a highly lethal disease
- Global challenges of utilization of, and access to, the recommended complete PEP regimen components
 - Supply, cost, and storage considerations

Perspectives on Rabies mAb Development



“More research, development and assessment are needed of suitable immunoglobulins or alternatives, such as human monoclonal antibodies, in rabies prophylaxis to ensure wider access to passive immunization at a reduced cost.”

- WHO Expert Consultation on Rabies. Second Report

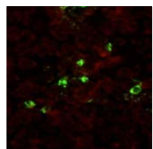


Issues in Assessing Activity of Rabies mAb as a Component of the PEP Regimen



Nonclinical Data

- Breadth of coverage vs diverse rabies virus strains
- Selection of mAb dosing regimens for initial clinical evaluations



Serologic Assays

- Passive protection during first few days of PEP
- Effects on rabies vaccine response



Clinical Trials

- Non-rabies-exposed population
- Suspected rabies-exposed population

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 (level and timing) are most predictive of protection after rabies-exposure?



Clinical Trials with Rabies mAb

Suspected Rabies-Exposed Population (1)

- What is the best achievable understanding from clinical trials in the suspected rabies-exposed population that a novel rabies mAb product provides protection from developing a lethal disease?
 - Important not only because of statutory regulatory needs for evidence supporting efficacy, but also important for public health and clinical decision-making.
- Hypothetical trial designs and considerations of trial endpoints will be presented to invite discussion on studying and interpreting the contribution of rabies mAb to PEP regimen
 - Superiority, non-inferiority, other possible trial designs
 - Mortality, other measurements (e.g., serology)

Clinical Trials with Rabies mAb

Suspected Rabies-Exposed Population (2)

Challenges in assessing passive-antibody contribution to PEP regimen

- Multiple factors affect risk of rabies after suspected exposure, such as:
 - Was the biting animal rabid?
 - Was the animal shedding rabies virus?
 - How close is the bite to the nervous system?
 - Could the bite site be promptly identified and thoroughly cleaned?
 - Is appropriate rabies vaccination series initiated and completed?
 - Is passive antibody delivered appropriately?

Objective of effective PEP is to decrease risk of developing rabies, but the effect of any one factor on this risk (including rabies mAb) may be hard to measure in any feasible clinical trial – and possibly even harder to accurately deduce from less-controlled use and experience.

Ethical Considerations

- What are important ethical considerations when designing clinical trials of a rabies mAb-based PEP product as an alternative to available hyperimmune globulins?
- What are the ethical considerations for enrollment of children in rabies mAb clinical trials?

Questions to Consider

- What can be learned from:
 - animal data?
 - serologic data?
 - WHO, Industry, and Academic experiences?
 - clinical trials?
- What is the nature and strength of data supporting direct links between any specific *in vitro*, animal, or serologic assessments and contribution of a specific component and dose of PEP to human clinical outcomes?
- What are the research gaps in understanding the contribution of rabies mAb to the PEP regimen?
- What are potential uses and limitations of possible clinical trial designs?
- What are ethical considerations in rabies mAb trial designs?

“It is better to debate a question without settling it than to settle a question without debating it.”

– Joseph Joubert, French essayist