Rabies immune globulin

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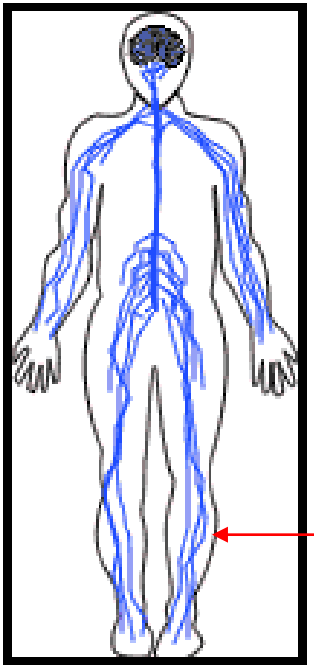
Viral pathogenesis of rabies

- Neurotrophic virus
  - Enters peripheral nerves
  - Travels centripetally to Central Nervous System
  - Flows centrifugally to innervated organs, including salivary glands
- Incubation period usually weeks to months
- Death typically within 2 weeks of illness onset

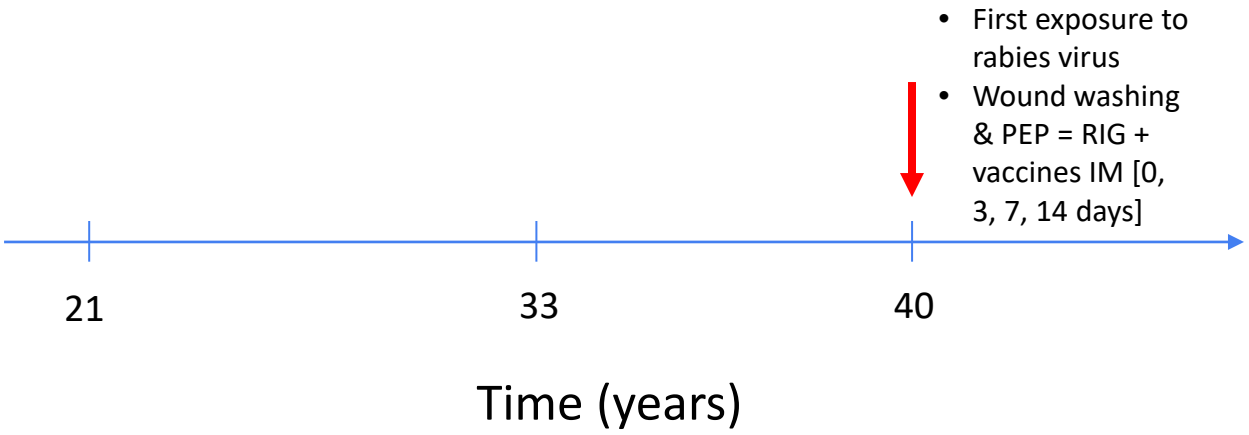


Role of rabies immune globulin (RIG) in preventing rabies

- Provide passive immunity before vaccine-induced humoral immunity occurs
- Given only to persons who have not received PrEP or previous PEP
- Does not negate the need for PEP vaccines because at least some rabies virus is expected to travel to the CNS

Indications for Rabies Immune Globulin

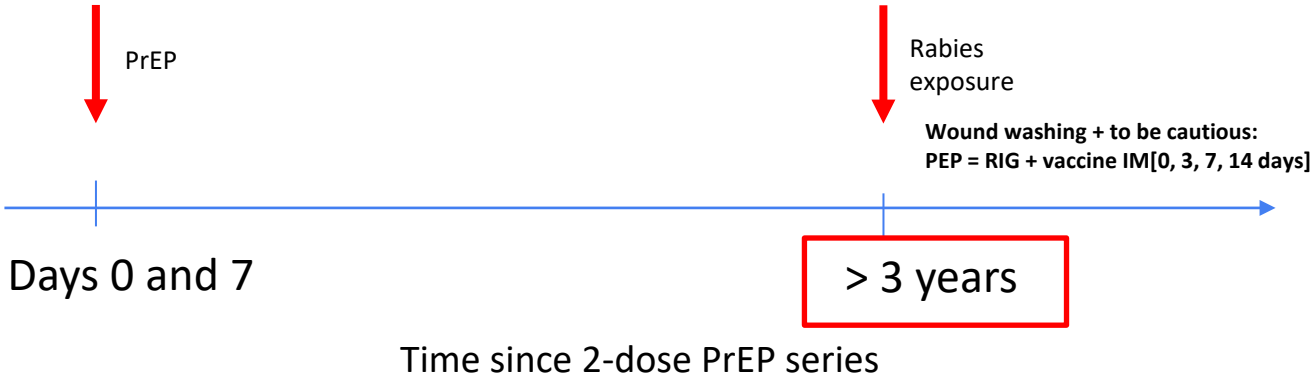
A) Persons who did not previously receive complete series of recommended PrEP or PEP



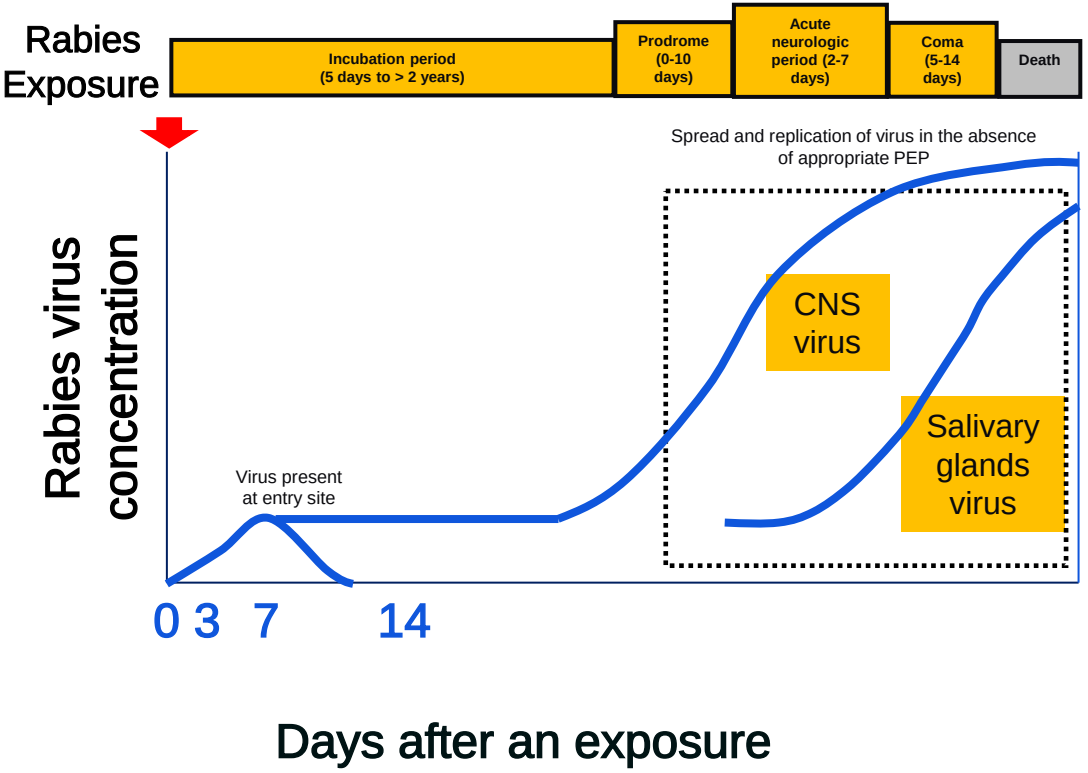
Indications for Rabies Immune Globulin

B) For persons who received previous 2-dose PrEP but:

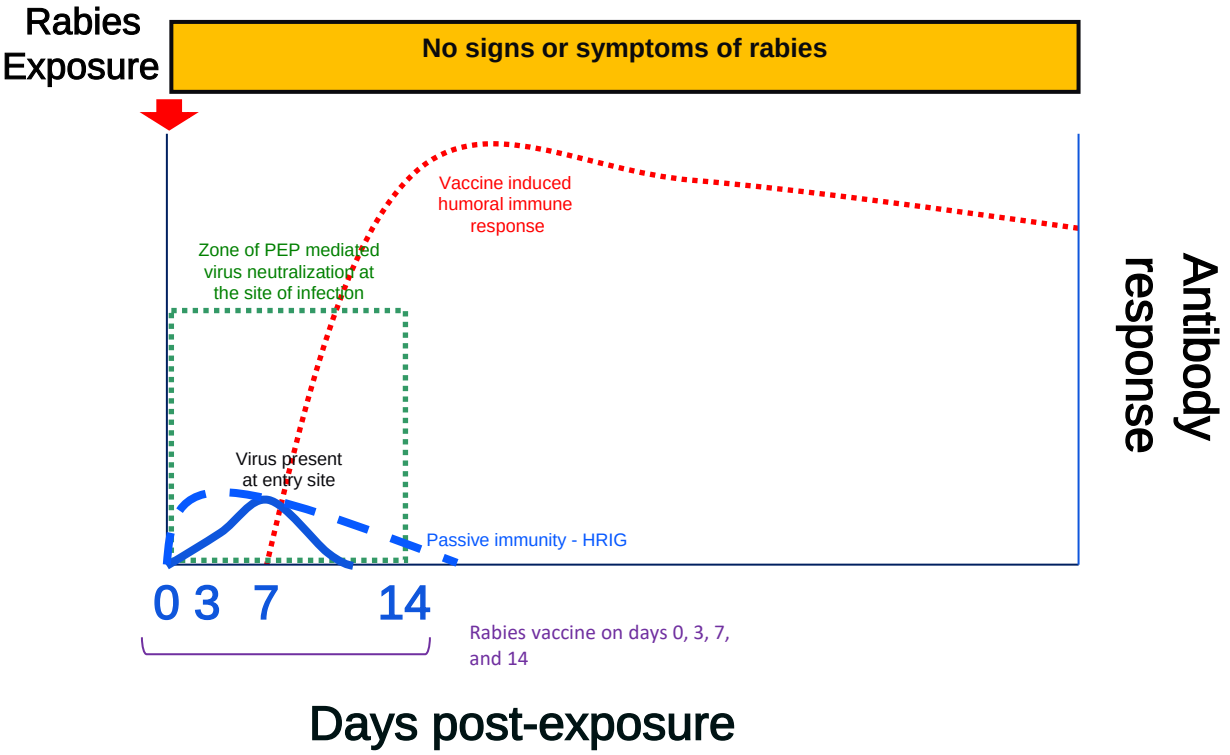
Did not receive titer or booster within 3 years (newly passed ACIP recommendations)



Rabies virus concentration without PEP



Rabies antibody response with PEP



2008 ACIP recommendations

- RIG products licensed in U.S. equally efficacious: HyperRab™ S/D and Imogam® Rabies-HT
- RIG administration within first 7 days of initiation of first rabies vaccine
- Administer 20 IU/kg, regardless of age
- Infiltrate maximal amount around wound that is anatomically feasible
- Remainder should be administered IM at location different from where vaccine is administered
- For large / multiple wounds, RIG can be diluted

2018 WHO considerations

- RIG in limited supply internationally
  - It is estimated that worldwide, <2% of persons with serious wounds (i.e., WHO Category III), receive RIG
  - RIG is very expensive

- Dog bites are most common rabies exposures
  - Wounds are large
  - Large proportion of RIG infiltrated around wound
  - Benefits from IM administration of remaining RIG may be limited

2018 WHO Position Statement

- Prioritize limited RIG
  - High risk (WHO Category III) exposures
  - Multiple bites
  - Deep wounds
  - Bites to highly innervated body parts
  - Persons with severe immunodeficiency
  - Exposures from confirmed or probable rabies case
  - Exposures from bats
- Limit RIG infiltration to RIG that can be infiltrated into and around the wound; no IM administration of leftover
- Maximum dose: 20 IU/kg
- Dilute RIG if there are multiple wounds

Human immunoglobulins licensed in U.S.

Product name	Manufacturer	Administration	Potency	Dose
Imogam®	Sanofi Pasteur	Infiltrated around wound and remainder administered intramuscularly	150 IU/mL	20 IU/kg
Kedrab™/ Kedrion	Biopharma and Kamada Ltd		150 IU/mL	20 IU/kg
HyperRab™ S/D	Grifols		150 IU/mL	20 IU/kg
HyperRab®			300 IU/mL	20 IU/kg

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ACIP WG considerations

- Two newly licensed RIGs: Are these new formulations or new products?

- RIG administration limited to wound
  - What is the data?
  - In the U.S., exposure wounds are often small (i.e., from bat). What are the U.S. implications?

- Is there data to support any other changes to RIG recommendations?

Newly licensed RIG products in U.S.

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Kedrab™/ Kedrion

- Licensed by FDA in 2017
- Indicated for
  - Passive, transient post-exposure prophylaxis
  - To persons of all ages
  - Given immediately after contact with a rabid or possibly rabid animal

- Clinical study design and trial results similar to previously licensed RIG products
- No referral of BLA submission was made to Blood Products Advisory Committee because no concerns

HyperRab®

- Licensed by FDA in 2018
- Indicated for PEP along with rabies vaccine
- Higher potency formulation of HyperRab™ S/D
  - Greater concentration of anti-rabies virus antibodies within each mL of volume
  - Less volume needed to administer recommended amount
- No FDA post-licensure requirements because considered to be new formulation (not new product)
- Improved production and manufacturing processes over the years
- Requires dilution with Dextrose 5% in Water (D5W) rather than normal saline

WG Assessment of Kedrab™ and HyperRab®

- Both prepared from plasma of donors who were hyperimmunized with rabies vaccine
- Safety and efficacy: Similar to previously licensed RIGs
- WG conclusions
  - Newly licensed products are not “new”
  - Desirable to have multiple licensed RIG products because shortages have occurred
  - HyperRab® is twice as concentrated resulting in less volume administered compared to other RIGs
  - Products equally efficacious so WG
  - No preferential recommendation of a specific RIG

Selection of RIG product

- Indications same for all
- More concentrated product could be preferable for small wounds (e.g., those from a bat bite)
- Given differences in potency between products, oversight needed to ensure correct volume administered for a particular product
- Clinicians should be aware that D5W is the recommended diluent for HyperRab® even though it is not provided with the product

- Individual facilities can determine which product to stock

WG discussions about RIG administration around wound

U.S. and RIG considerations

- Role for RIG
  - Studies indicate it can be advantageous
  - It is not difficult to access in U.S.
- Most rabies cases are from bat exposures
  - These create small or barely visible wounds
  - Very little RIG is administered around a wound
- Immunogenicity data suggests that IM RIG is detected in sera 24 hours later; there may be benefit

Pathophysiology

- RIG infiltrated around wound likely remains at site of injection
  - Limited data cited in WHO Position Statement*
  - Unclear whether IM administration of RIG provides significant benefit

- Data insufficient for WG to propose change to current ACIP recommendations

*Madhusudana et al, Saesow et al, and Wilde et al included in background documents

Conclusion

- Two newly licensed RIGs (2017): Are these new formulations or new products? New formulations

- RIG administration limited to wound
  - What is the data? WHO considerations different from ACIP's
  - In the U.S., exposure wounds are typically small (i.e., from bat). What are the U.S. implications? Small wounds would result in very small (if any) RIG infiltrated around wound

- Is there data to support any other changes to RIG recommendations? No changes to any RIG recs; clinical guidance will be presented at the October ACIP meeting

Acknowledgements

- Rabies WG
- RIG product sponsors
  - Grifols
  - Biopharma and Kamada Ltd

Thank you