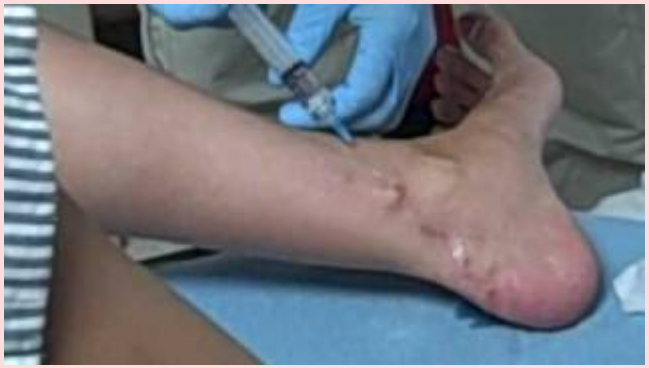
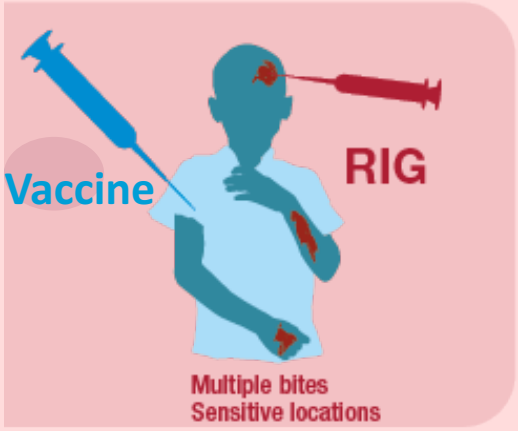
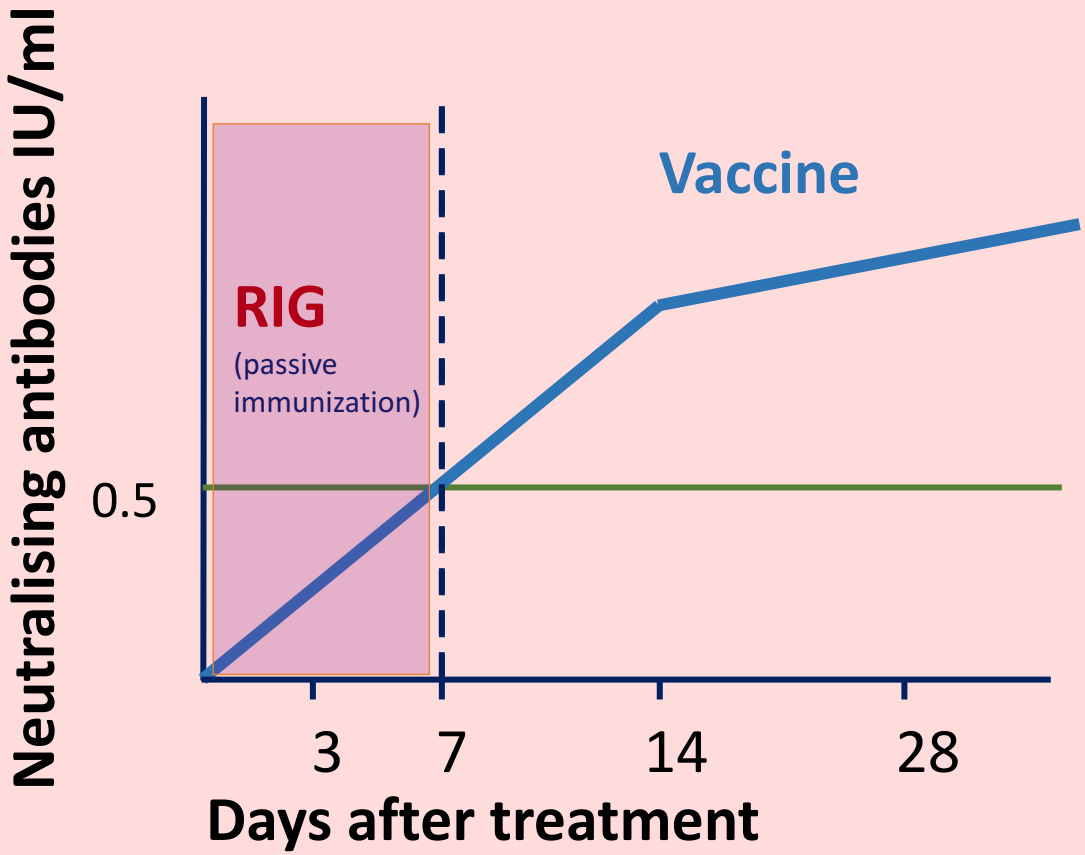
Rabies Immunoglobulins (RIG)

Questions 10, 11, 12, 13, 14



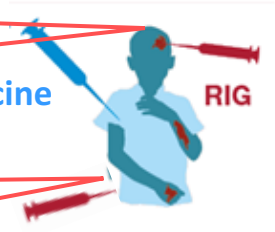




Summary current recommendations on Rabies Immunoglobulins

- Dose for hRIG | eRIG = 20 | 40 IU/ kg body weight
- Mode of RIG administration:

1. RIG to all wounds
2. Rest RIG IM



- hRIG is the preferred product for severe exposures (but eRIG less expensive)
- eRIG carries a small risk of anaphylaxis, no need for skin test

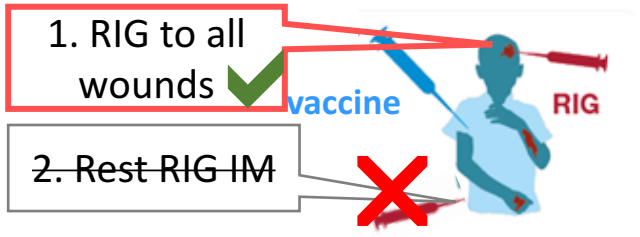
Question 10: Are there novel approaches to **RIG (-sparing) injection** versus current practice as part of PEP for category III exposed patients?

Question 11: Is there clinical equivalence in the **safe use of eRIG** compared to hRIG in category III exposed patients?

Question 12: Is there clinical equivalence in the **efficacious use of eRIG** compared to hRIG in category III exposed patients?

Question 10, 11, 12: Review of new evidence

- Review of 3 RCT, 13 observational studies, country data & modelling estimates
- Main findings:
  - Evidence suggests RIG is **most efficacious at the wound site**:

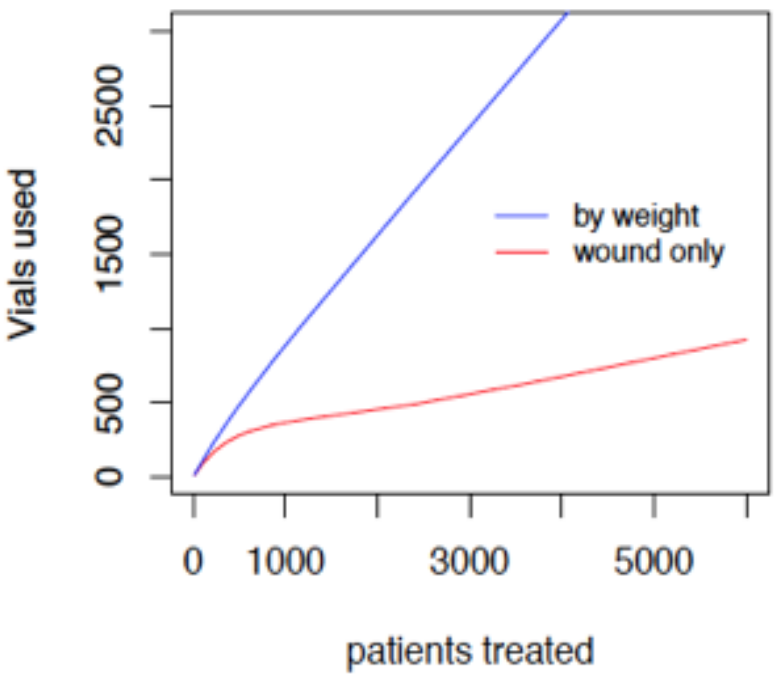


  - To **avoid interference** with vaccine-induced rabies virus neutralizing antibodies maintain calculation for maximum RIG dose to wound
  - eRIG/F(ab')$_2$ are now highly purified, high affinity
    - **clinically comparable to hRIG**
    - Adverse reactions ↓↓ (~ incidence for Penicillin)

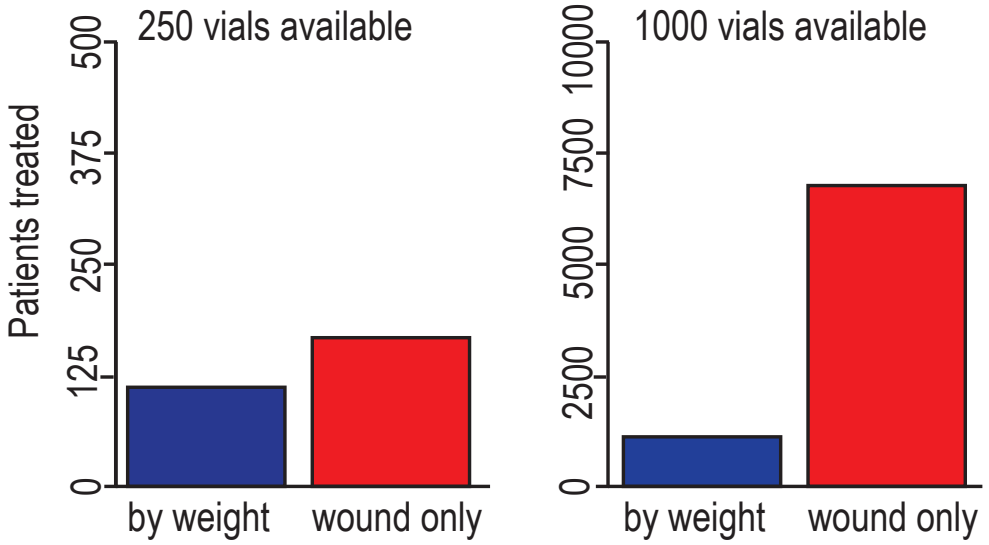
Public health impact of change in RIG administration mode

(model estimates)

a) By levels of patient throughput



b) # of patient treated in case of shortage



2010 WHO recommendations on RIG administration (blue)

RIG injection at the site of the wound only, up to max based on weight (red).

Key problem:

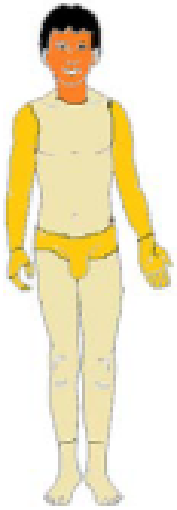
The high cost, low availability and supply, batch-to-batch variation affecting efficacy, uncertain quality, short shelf life and correct administration of RIG are barriers to implementing the standard set by WHO for PEP in category III rabies exposures.

Question 14: In cases of RIG shortage and constraints, can **subcategories of patients** be identified who should be given **highest priority for RIG** administration?

Question 13: Can **monoclonal antibodies** be safely and efficaciously administered in category III exposed patients compared to standard RIG?

Question 14: Details new evidence

Transmission risk
(Cleaveland et al. 2002)



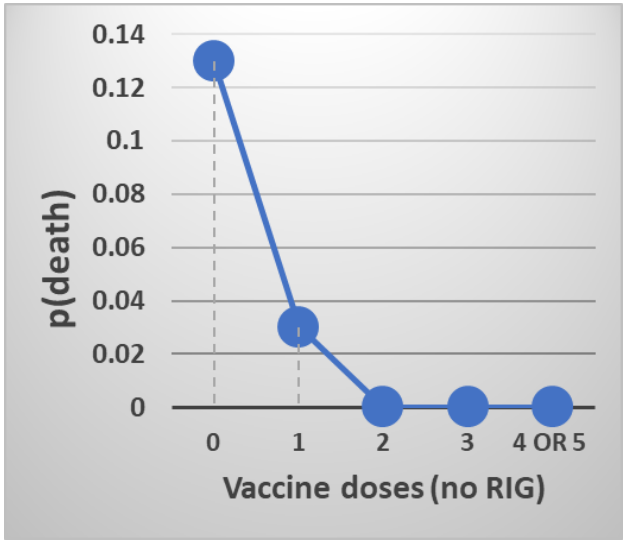
30-60%

15-40%

15-40%

Probability of death in rabies exposed & number of vaccine doses (no RIG)

Tanzanian data n= 2,196



Cambodian data n= 265

Preliminary data (2003-2014) ***0 deaths:***

- Among 62 persons exposed to rabid dogs
- Among 203 persons exposed to untested, but sick dogs
- Even though **NO RIG**

Interventions improving chance of survival after a rabies exposure:

- Thorough wound washing + same day vaccine administration
  → **99% patients survived even without RIG**
- Use of quality vaccine
- Completion of full course of PEP regimen

Question 13: Details new evidence

Considerations for rabies mAbs to complement blood derived RIG products in rabies PEP	
Advantages	Limitations
Cell culture derived antibodies. Product contains only immunologically relevant defined epitopes	Investment in discovery and pre-/clinical trials with documented clinical outcome.
Possibility of mAb cocktails with at least two non-overlapping epitopes to improve efficacy and breadth of neutralization	Single mAbs recognize one epitope-risk for escape variants. mAb cocktails with two ore more distinct, non-overlapping epitopes
Minimal batch to batch variability Scalable technology Reduced activity units required to confer protection Possibility for more concentrated products	Regulatory approval processes for rabies mAbs not clearly defined. Long term post-market evaluation needed to validate effectiveness in preventing death
Cost-effective long term and production costs will decrease as technology improves.	Unit pricing needs to be competitive to provide incentives to countries to uptake and further expand market

Single epitope rabies mAb product, produced by Serum Institute India Ltd, has been **licensed by Indian regulatory authorities** (available end 2017- beginning 2018)

- Recognizes broad range of viruses - conferred protection in animal models.
- Safety established (minimal allergenicity, hypersensitivity reactions) and comparable potency to hRIG
- Post-market evaluation is on-going to determine effectiveness in reducing human rabies deaths
- Slight risk for virus escape mutants in the American region.

Rabies mAb cocktail from Zydus Cadila Pharmaceuticals is **in clinical trials**.

Conclusion RIG questions

- Local infiltration of RIG, **maximal amount into the wound is most effective**
- **eRIG and hRIG** are considered **clinically equivalent** for rabies virus neutralization at the wound site
- **Skin testing** prior to administration of eRIG should be **abandoned**
- Thorough **wound washing** + immediate administration of the first dose of **vaccine** (+ completion of the PEP regimen) can **save up to 99% of bite victims from fatal rabies**
- The newly licensed **mAb** product may provide an opportunity to **improve access to RIG** products
  - Future improvements: mAb 'cocktail product' (> 1 mAb)
- **Post-marketing surveillance** is needed for both, RIG and mAb