# THE NEW WHO POSITION ON RABIES IMMUNIZATION

*Towards Rabies Elimination in Asia-Pacific*

**Bangkok, Thailand, 25 September 2018**

**Bernadette Abela-Ridder, Kaushi Kanakege**

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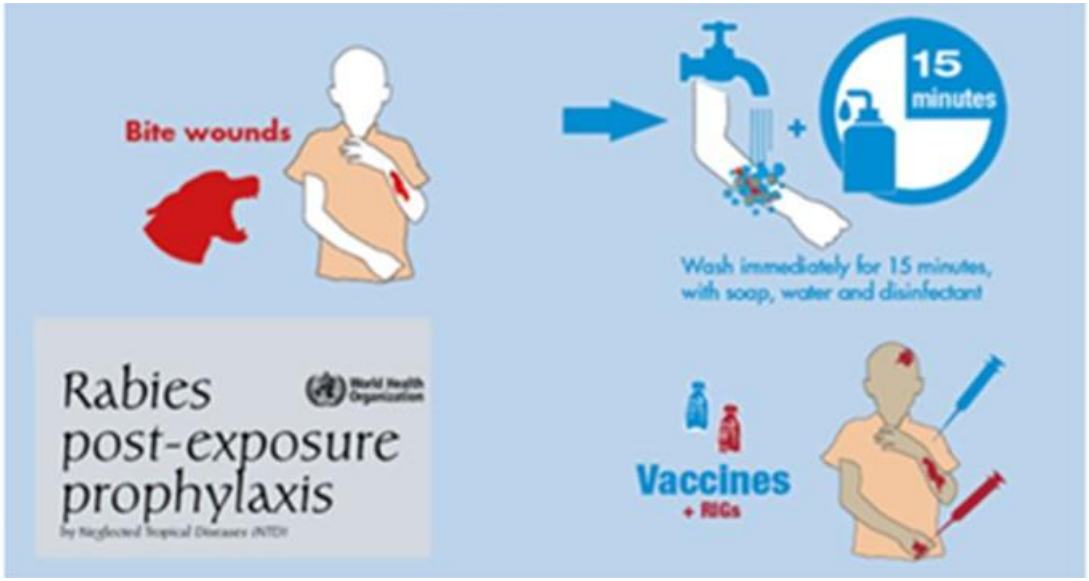
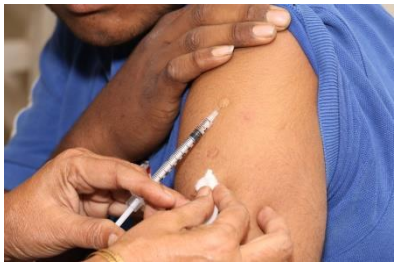
# The 2018 WHO position on rabies immunization



# Review & update rabies immunization policy to best evidence and practice

- In depth analysis of new evidence (July 2016-July 2017):
  i. Systematic scientific literature reviews
  ii. Information from reports and country programmes
  iii. Data supporting a change in practice / underpin established new practice
- Report to SAGE (October 2017)
- Publication of the WHO position paper on rabies vaccines considering feasible & safe recommendations and cost-effective practices (April 2018).



http://www.who.int/immunization/policy/sage/sage_wg_rabies_jul2016/en/

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# Key updates WHO position on rabies immunization:

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

Contents

Rabies vaccines: WHO position paper – April 2018

Introduction

Vaccins antirabiques: Note de synthèse de l'OMS – avril 2018

Introduction

- Exposure categories
- Advocacy for intradermal vaccine administration
- Expedited PEP/PrEP schedules
- Prudent use of RIG
- Monoclonal antibodies (mAbs) as a viable alternative to RIG
- Prioritization of high risk patients, if shortage of biologics

http://www.who.int/rabies/resources/who_wer9316/en/

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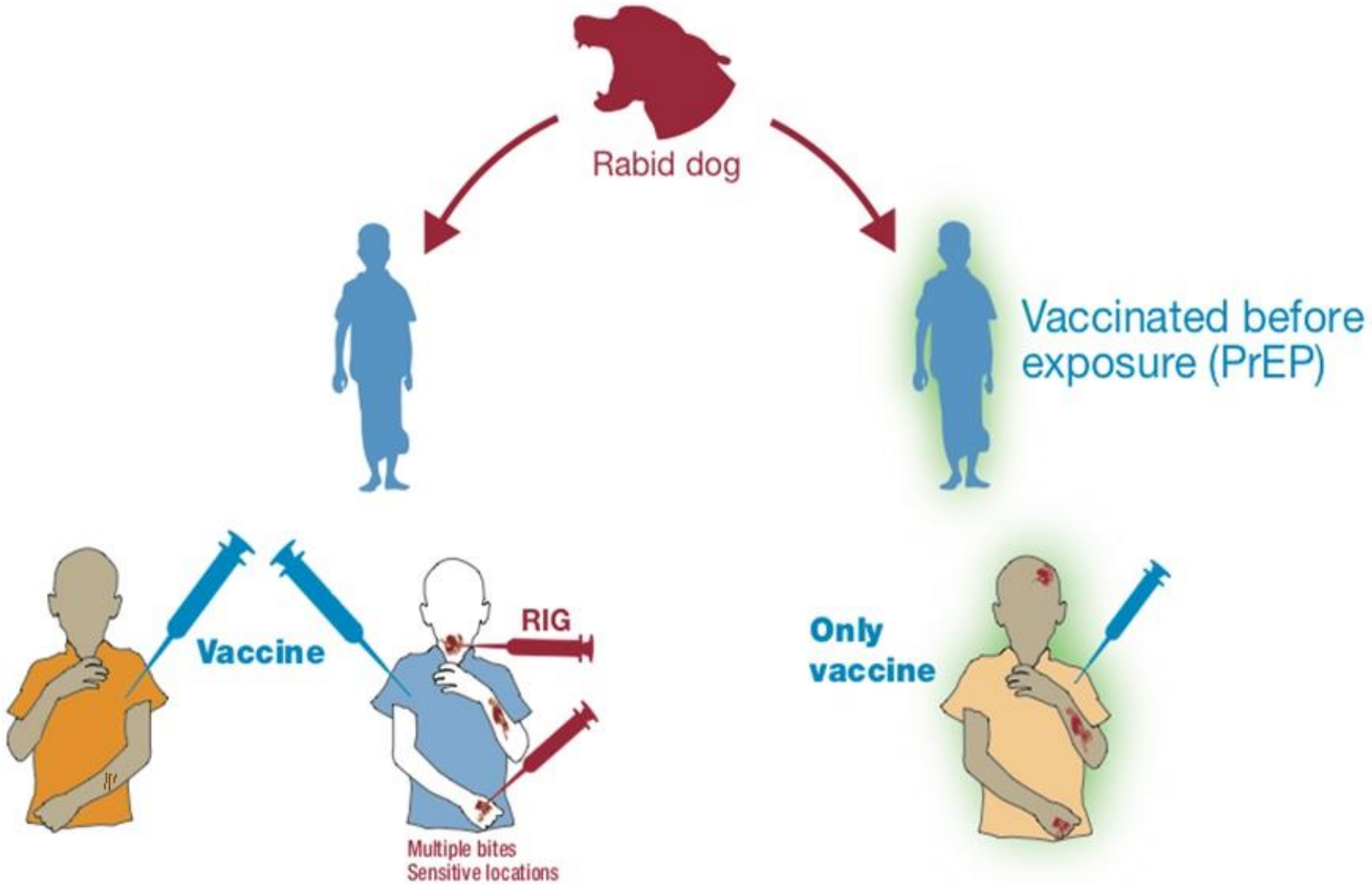


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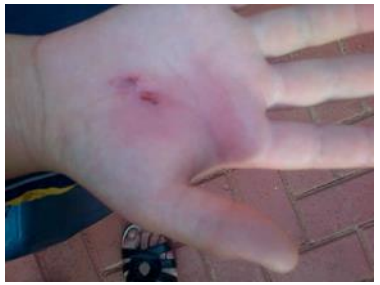
# WHO rabies exposure categories

The following categories describe the risk of a rabies virus exposure according to the type of contact with the animal suspected of having rabies.

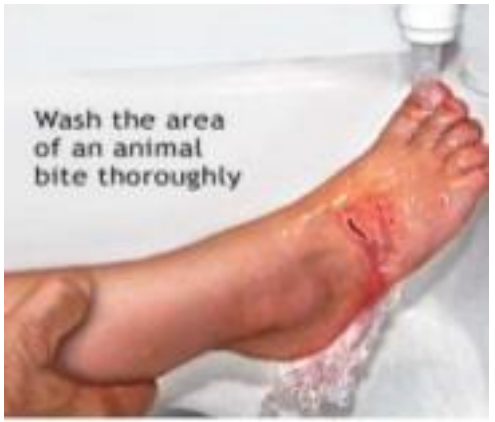
- **Category I** touching or feeding animals, animal licks on intact skin (**no exposure**);
- **Category II** nibbling of uncovered skin, minor scratches or abrasions without bleeding (**exposure**);
- **Category III** single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks, exposures due to direct contact with bats (**severe exposure**).

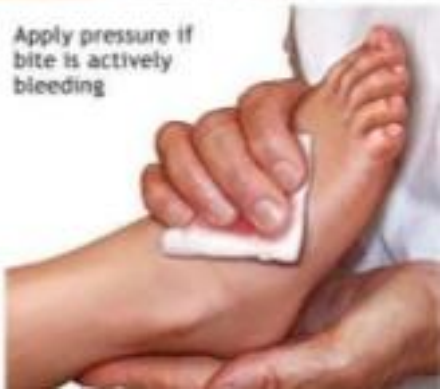


# Components of PEP

- PEP or Post-exposure prophylaxis after a potential exposure to rabies virus

- PEP **always** includes:
  - Wound washing and wound care
  - A series of rabies vaccine injections should be administered **immediately** after an exposure
- PEP sometimes includes:
  - Administration of rabies immunoglobulins (RIG)
    - in severe category III exposures
    - in category II exposures to bats



# PEP for Immunologically naive individuals (all ages):
## WHO-recommended rabies PEP regimens

| Regimen | Summary | Day (number of sites) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 0 | 3 | 7 | 14 | 21 | 28 |
| ID | 2-sites ID on days 0, 3 and 7 (IPC regimen) | ✓ (2) | ✓ (2) | ✓ (2) | | | |
| IM | 1-site IM on days 0, 3, 7 and between day 14-28 (Essen 4-dose regimen) | ✓ (1) | ✓ (1) | ✓ (1) | ✓ (1) | | |
| IM | 2-sites IM on days 0 and 1-site IM on days 7, 21 (Zagreb regimen) | ✓ (2) | | ✓ (1) | | ✓ (1) | |

Previously WHO-recommended PEP regimens are still valid, but are less cost-effective!

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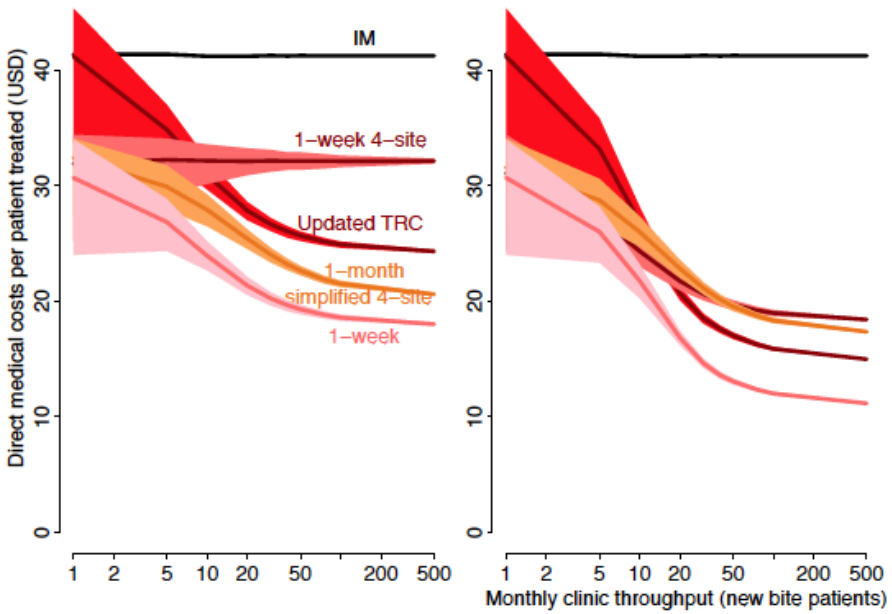
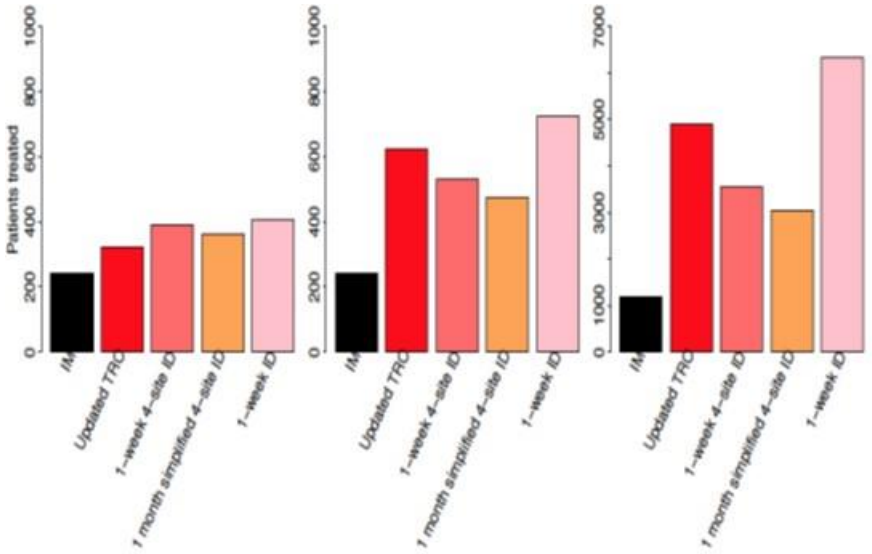
# Modelling cost-effectiveness of different PEP regimens

Hampson et al. :Modelling to inform prophylaxis regimens to prevent human rabies (https://doi.org/10.1016/j.vaccine.2018.11.010)

0.5 ml vials 1.0 ml vials




250 vials available 1000 vials available 3000 vials available




**Direct medical costs per rabies death averted** for selected ID regimens in relation to clinic monthly throughput

**Additional number of patients treated / year** under different, selected regimens, given **limited vaccine availability**

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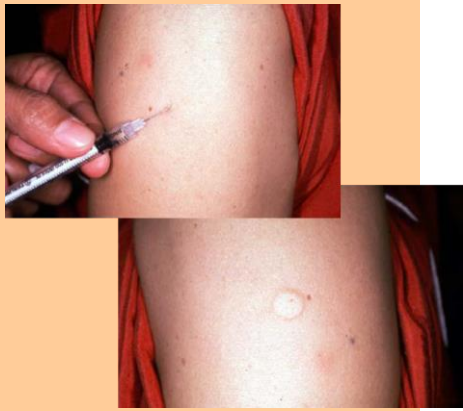
# Even if used off-label, the WHO encourages ID administration of PEP over IM.

***Because increased use of ID regimens could:***



- ❑ *prevent vaccine shortages*
- ❑ *Reduce direct & indirect cost for PEP*
- ❑ *increase the number of patients treated*
- ❑ *increase the overall accessibility of rabies PEP.*

# PEP for previously immunized individuals (all ages)

- Not indicated, if PEP already < 3 month ago
- People who had ≥ 2 rabies vaccine administrations (as PEP or PrEP) at some point in life
- RIG is contraindicated!
- Wound washing is key!

| Regimen | Summary | Day (nb of sites) | |
|---|---|---|---|
| | | 0 | 3 |
| ID | 2-sites ID on days 0 and 3 | (1) | (1) |
| ID | 4-sites ID on day 0 | (4) | |
| IM | 1-site IM on days 0 and 3 | (1) | (1) |

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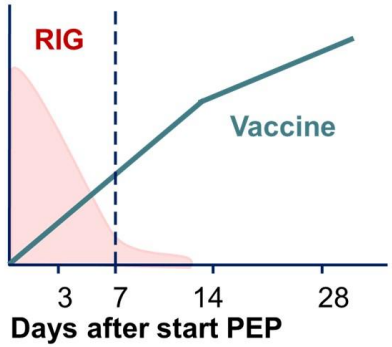
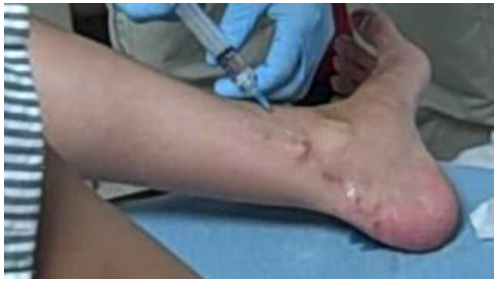
# Rabies Immunoglobulins (RIG)

- RIG **neutralizes virus locally** at the exposure site
- **hRIG and eRIG** are considered to have **similar clinical protective effect**
- Don't give RIG > d7 after 1st dose of vaccine, **interference** with vaccine-induced neutralizing antibodies
- A single **monoclonal antibody** (mAb) product against rabies, licensed in India in 2017, has been demonstrated to be safe and effective in clinical trials.



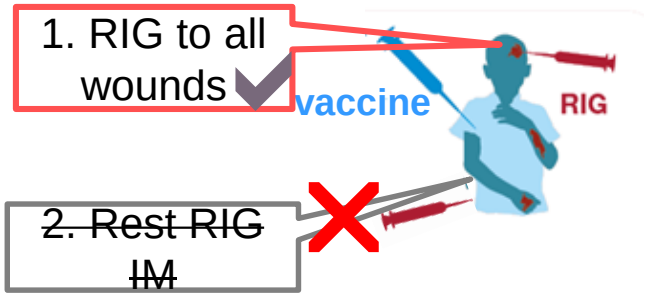
# *Administration of RIG*

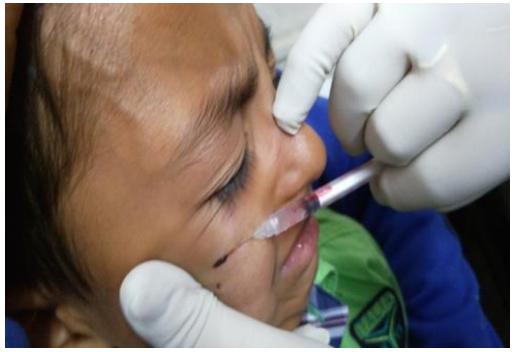
- RIG is indicated for **category III rabies exposures**
- **RIG** should be given **only once in life**, on or as soon as possible after, the initiation of PEP (not > day 7).
- **RIG is infiltrated into and around the wound**
- The maximum dose calculation for **eRIG is 40 IU/kg** body weight, and for hRIG **20 IU/kg** body weight
- **No skin testing** before **eRIG** administration as unreliable prediction of adverse effects (~ incidence like for Penicillin)



# *Administration of RIG into the wound!*

- RIG is **most efficacious at the wound site,** little to no effect, if injected IM distant to the wound!



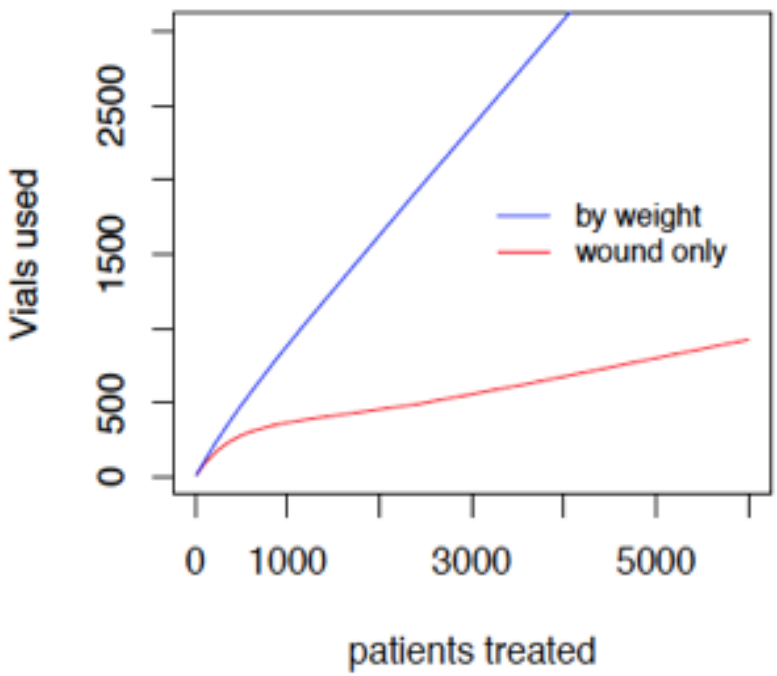



- Infiltrate as much of the RIG dose possible **into and around ALL wounds** (dilute if necessary)
- Aseptic conditions given, the maximum calculated RIG **dose/vials can be fractionated** into smaller, individual syringes to be used for other patients

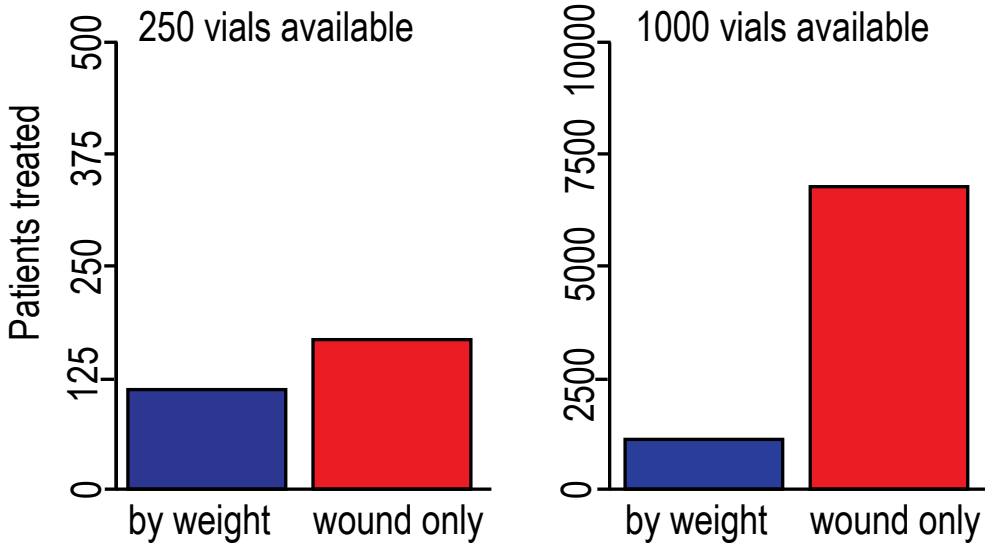
# Public health impact of new RIG administration mode

(model estimates)

**a) By levels of patient throughput**




**b) # of patients treated in case of shortage**




**2010 WHO recommendations: RIG administration to wound & distant IM** (blue)
**2018 WHO recommendations: RIG injection at the site of the wound only** (red).

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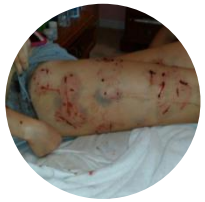
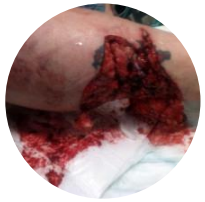
# RIG Prioritization in case of shortage



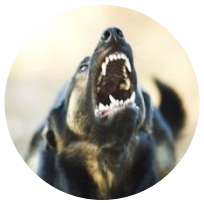
Multiple bite wounds



Deep wounds

Bites to head & highly innervated parts of the body

Patients with severe immunodeficiency



History of an animal bite indicative of confirmed or probable rabies

- Rabies vaccines should never be withheld regardless of RIG availability
- If RIG is unavailable on the 1st visit, administration can be delayed by max. 7 days from the date of the first vaccine dose (day 0)

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# Pre-exposure prophylaxis (PrEP)

- For individuals **at high risk of rabies virus exposure**:
  - These include sub-populations in highly endemic settings with limited access to timely and adequate PEP
  - Individuals at occupational risk
  - Travellers to remote areas who may be at risk of exposure
- Consider in sub-populations living in **remote**, rabies-endemic areas, where the **dog bite incidence is >5% per year** or vampire bat rabies is present.
- **PrEP schedules**:
  - 2-site ID vaccine administered on days 0 and 7.
  - 1-site IM vaccine administration on days 0 and 7.

# WHO pre-qualified human rabies vaccines

## as per Aug 2019

| Vaccine | Brand | Producer | Country |
|---|---|---|---|
| ~~PCEC~~ | ~~**Rabavert**~~ | ~~GSK~~ | ~~Germany~~ |
| PCEC | **Rabipur** production stopped | formerly Chiron Behring Vaccines Private Ltd | India |
| PVRV | **Verorab** | Sanofi Pasteur | France |
| PCEC | **VaxiRab N** | Cadila Health Ltd | India |
| PVRV | **RABIVAX-S** | Serum Institute of India | India |

# New WHO position on rabies immunization:

## *Safety - programmatic savings - feasibility*

| Topic | 2010 | 2018 |
|---|---|---|
| **PEP regimen duration** | 3-4 weeks<br>4-5 visits | **1-2 weeks**<br>**3-4 visits** |
| **Vaccine savings PEP** | ID: 0.8 ml<br>IM: 5 vials | ID: **-20%** (0.6 ml)<br>IM: **-20%** (4 vials) |
| **PrEP regimen duration** | 3 weeks | **1 week** |
| **RIG infiltration mode** | Wound + distant IM<br>No skin test eRIG | Wound only<br>**- 40%** RIG vials<br>No skin test eRIG |
| **RIG allocation** | All category III exposures | High risk cat. III exposures<br>**- 60 to 90%** need RIG |

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