Monoclonal antibodies for rabies post exposure prophylaxis

World Health Organization

2018 Global Vaccine and Immunization Research Forum

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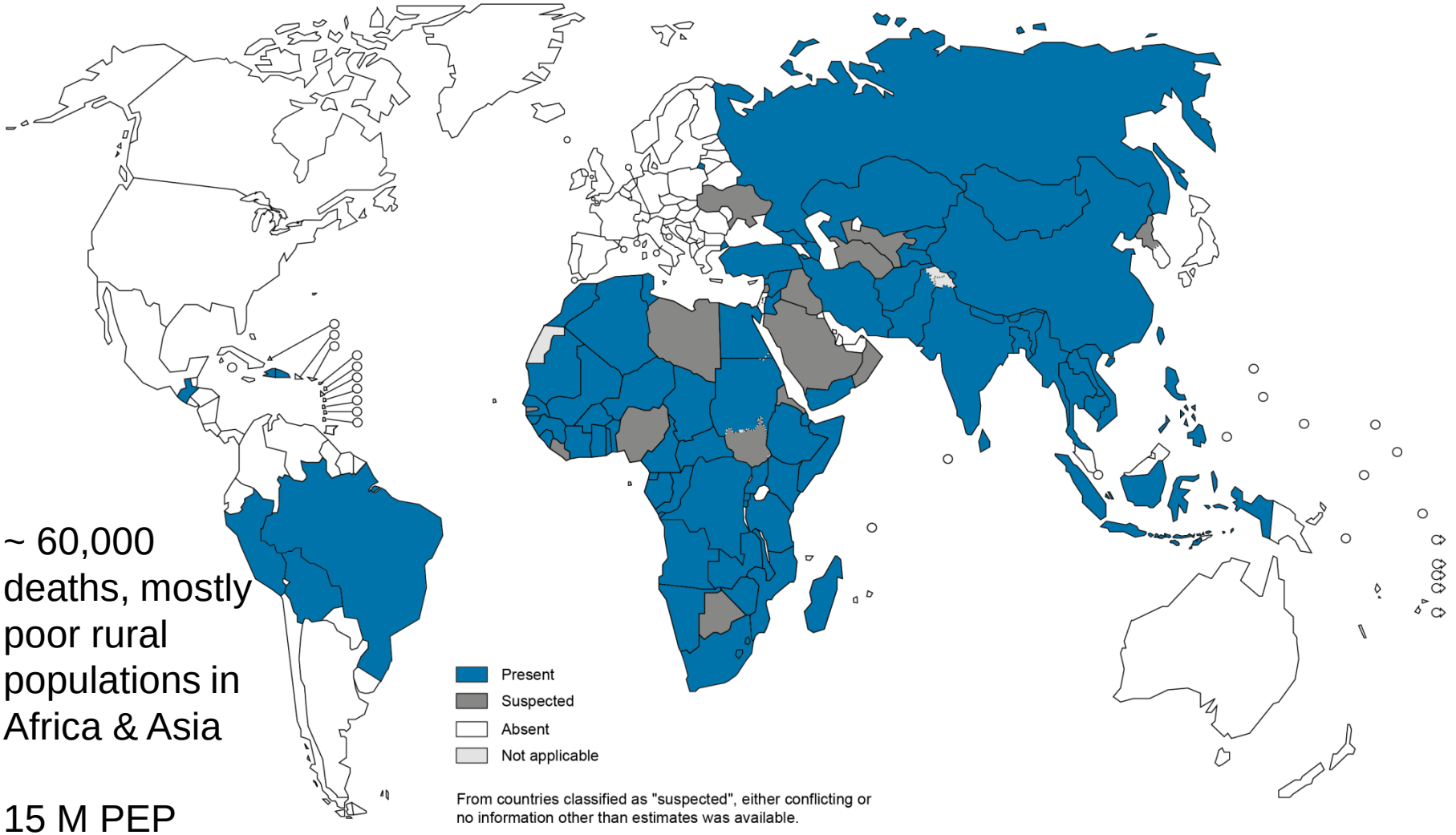
Presence of dog-transmitted human rabies based on most recent data points from different sources, 2010-2014



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

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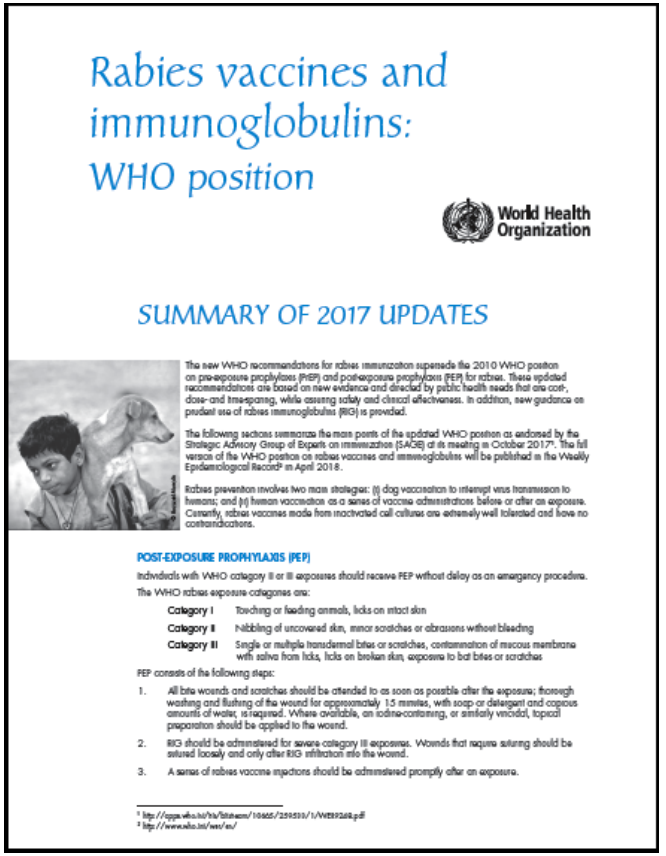
Passive immunization in rabies Post-Exposure Prophylaxis (PEP)

Severe **category 3** exposures:

- Immediate wound washing + immediate vaccination & **rabies immunoglobulin** (RIG injected into the wound to neutralize virus while immune response to vaccine is mounting).
- New <u>cost-effective</u> WHO recommendations:
  - Vaccines: 2-site ID on days 0, 3 and 7 *(previous recomms still valid)*
  - RIG: max dose 20 IU/Kg (hRIG), 40 IU/Kg (eRIG), as much as possible into wound; remainder of calculated dose does not need to be injected at a distance from the wound & can be saved. If limited RIG, allocation should be prioritized based on risk
  - Will include considerations for the use of mAbs



Rabies vaccines and immunoglobulins: WHO position

World Health Organization

SUMMARY OF 2017 UPDATES

The new WHO recommendations for rabies immunization supersede the 2010 WHO position on pre-exposure prophylaxis (PEP) and post-exposure prophylaxis (PEP) for rabies. These updated recommendations are based on new evidence and directed by public health needs that are safe, dose- and time-sparing, while assuring safety and clinical effectiveness. In addition, new guidance on prudent use of rabies immunoglobulins (RIG) is provided.

The following sections summarize the main points of the updated WHO position as endorsed by the Strategic Advisory Group of Experts on immunization (SAGE) at its meeting in October 2017[1]. The full version of the WHO position on rabies vaccines and immunoglobulins will be published in the Weekly Epidemiological Record[2] in April 2018.

Rabies prevention involves two main strategies: (i) dog vaccination to interrupt virus transmission to humans; and (ii) human vaccination as a series of vaccine administrations before or after an exposure. Currently, rabies vaccines made from inactivated cell cultures are extremely well tolerated and have no contraindications.

POST-EXPOSURE PROPHYLAXIS (PEP)

Individuals with WHO category II or III exposures should receive PEP without delay as an emergency procedure.

The WHO rabies exposure categories are:

Category I — Touching or feeding animals, licks on intact skin

Category II — Nibbling of uncovered skin, minor scratches or abrasions without bleeding

Category III — Single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks, licks on broken skin, exposure to bat bites or scratches

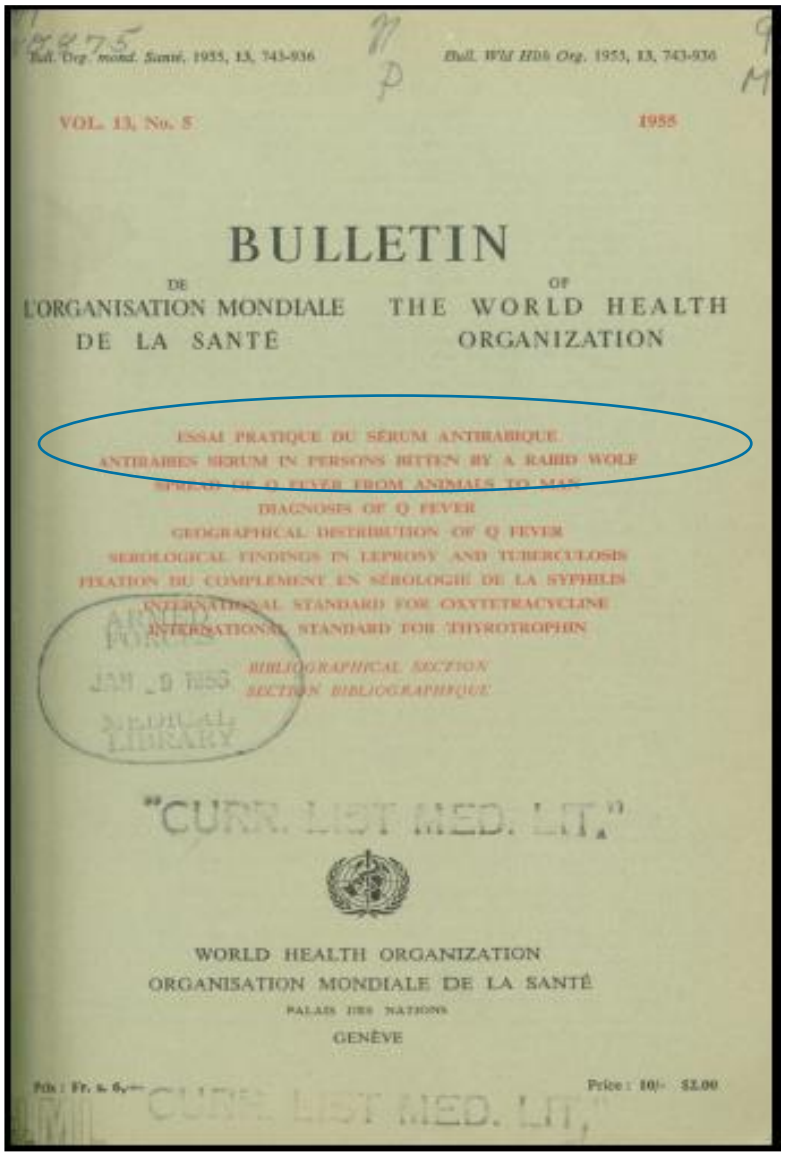
PEP consists of the following steps:

1. All bite wounds and scratches should be attended to as soon as possible after the exposure; thorough washing and flushing of the wound for approximately 15 minutes, with soap or detergent and copious amounts of water, is required. Where available, an iodine-containing, or similarly virucidal, topical preparation should be applied to the wound.
2. RIG should be administered for severe category III exposures. Wounds that require suturing should be sutured loosely and only after RIG infiltration into the wound.
3. A series of rabies vaccine injections should be administered promptly after an exposure.

[1] http://apps.who.int/iris/bitstream/10665/259539/1/WER9248.pdf
[2] http://www.who.int/wer/en/

Full version of updated WHO position (SAGE Oct 2017) will be published in WER in April 2018.

Historical "clinical development" of RIG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DE L'ORGANISATION MONDIALE DE LA SANTÉ

OF THE WORLD HEALTH ORGANIZATION

ESSAI PRATIQUE DU SÉRUM ANTIRABIQUE

ANTIRABIES SERUM IN PERSONS BITTEN BY A RABID WOLF

SPREAD OF Q FEVER FROM ANIMALS TO MAN

DIAGNOSIS OF Q FEVER

GEOGRAPHICAL DISTRIBUTION OF Q FEVER

SEROLOGICAL FINDINGS IN LEPROSY AND TUBERCULOSIS

FIXATION DU COMPLÉMENT EN SÉROLOGIE DE LA SYPHILIS

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Never evaluated in "phase 3" clinical studies

Iran 1954[1,2]: 29 ppl bitten by a rabid wolf, treatment started within 30h, 2 groups: vaccine alone or combination of serum & vaccine.

- Excluding those with less severe wounds, in the 18 severe: 3 of 5 who received vaccine alone died, of the 13 given both vaccine & serum, only 1 died
- The use of RIG with vaccine became the standard of care for category III PEP.

1. *Baltazard M, Bahmanyar M. Field trials with rabies vaccine on persons bitten by rabid wolves. Bull World Health Organ 1955; 13: 747–72.*
2. *Habel K, Koprowski H. Laboratory data supporting the clinical trial of anti-rabies serum in persons bitten by a rabid wolf. Bull World Health Organ 1955; 13: 773–79*

Limitations of blood-derived RIG

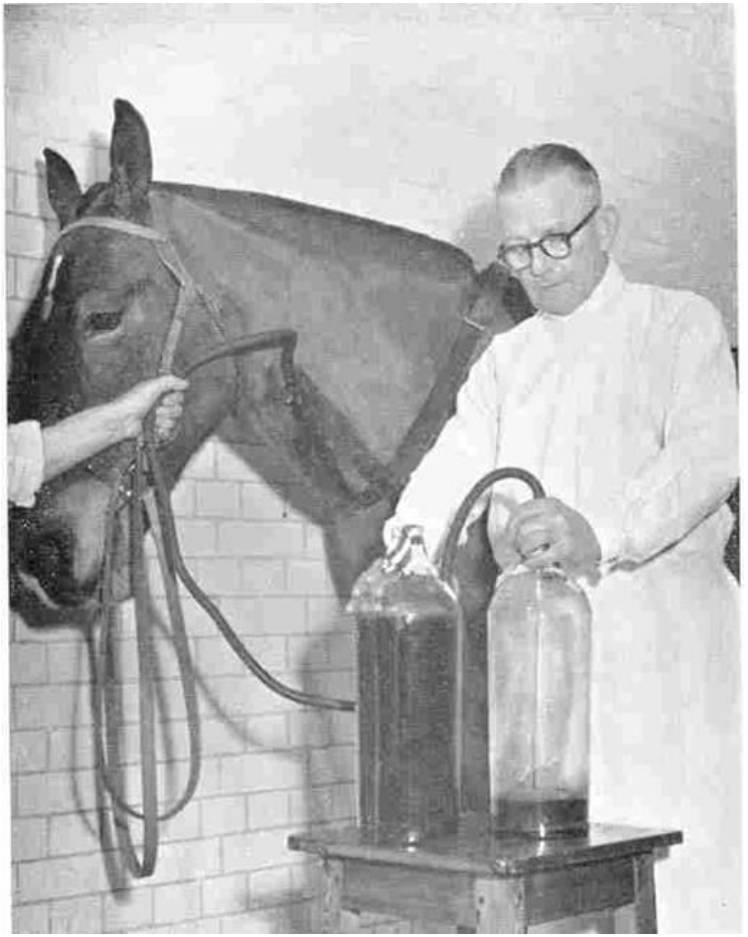
Availability: limited supply, short shelf-life, only 1-10% of patients who need it receive RIG

Affordability: expensive, especially HRIG $250-1,500, ERIG ~ $US 20, often paid out of pocket

Quality: batch to batch variation affecting efficacy

(*Safety*): ERIG: improved purification & safety, WHO no longer recommends skin-test prior to administration

Archaic



www.who.int/immunization/sage/meetings/2017/october/1_Background_paper_WG_RABIES_final.pdf

Monoclonal antibodies for rabies PEP

- Supplement supply of the passive immunization component of PEP
- Adequate supply (easier to produce, mass production, QC easier)
- Reduced production costs
- Reduces risks of adverse reactions
- Advantage of concentrated neutralizing mAbs
- More affordable than HRIG, cost comparative or even less than ERIG

Advanced mAb candidates

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Product	Manufacturer	Clinical trials	Comment
CL184	Crucell, Johnson & Johnson	Phase I (USA) completed, SRCTN18660493 Phase I/II (India) completed, SRCTN12693237 Phase II (USA) completed, NCT00656097 Phase II (India) completed, NCT01228383 Phase II (Philippines) completed, NCT00708084	Product development stopped, no further clinical trials planned (communication from Crucell 2016).
Rabishield	Partnership b/w MassBiologics & Serum Institute of India	Phase I (India) completed, CTRI/2009/091/000465 **Phase II/III (India) completed,** CTRI/2012/05/002709: 200 subjects, NI to RIG, proportion of subjects with RFFIT titre more than or equal to 0.5 IU/ml on Day 14 (Gogtay et al, CID 2018)	**Product licensed in India in August 2016,** commitment from SIIL for affordable pricing for DCs (20% more than ERIG)
Rabimabs	Zydus Cadila (MTA from WHO)	Phase I/II (India) completed, CTRI/2012/12/003225, CTRI/2015/06/005838 **Phase III (India) ongoing CTRI/2017/07/009038**: 308 subjects, NI to RIG, proportion of subjects with RFFIT titre more than or equal to 0.5 IU/ml on Day 14	Ph 3 initiated in August 2017, commitment for affordable pricing
SYN 023	Synermore Inc.	Phase II (USA) completed NCT02956746	Completion of ph 2 in January 2018, proposal to FDA for multi-national ph 3
Human Anti-Rabies MAb	M.T.T.I and NCPC (US & China)	Phase II ongoing www.mtarget.com/mm5/pdfs/pipeline/RabiesMonoclonalAnti.pdf	

FDA workshop July 2017

FDA workshop on "Developing Rabies Monoclonal Antibody Products as a Component of Rabies Post-exposure Prophylaxis", 17 July 2017.
www.fda.gov/Drugs/NewsEvents/ucm540832.htm

Brought together regulatory experts, developers of rabies mAbs, clinicians from bite centres in developing countries etc to discuss animal models, laboratory assays, and clinical trials.

Take home message:

- Serological/neutralization assays & hamster challenge model well established
- Neutralization should be explored across as many strains as possible
- Placebo unethical, superiority trials not feasible, non-inferiority RCT preferred
- Confirmed rabies exposure (logistically challenging & costly) – or powered adequately to take into account estimated exposure
- Larger the sample size, larger # of sites, increased cost, increase time
- Questions: Which NI margin? Which population? Simulated PEP in healthy volunteers? Dog-bite patients? When to include children? What end-points? Serology only? Survival outcome? Post-market surveillance?

Challenges of uptake/use

- Decision by policy makers to include mAbs in PEP?
  - SAGE recommendation, coming
  - Inclusion in the WHO essential medicines list
- Treatment guidelines needed
- Procurement/ supply
  - Registration in other countries
  - UN procurement/ bulk purchase
  - WHO Prequalification

Conclusions

- Rabies mAbs have an imporant role to play in supplementing the supply of RIG in in reducing the costs of rabies PEP
- One product is available in India and 2 others are in phase 3 clinical trials
- Next steps: ensure policy recommendations follow and facilitate uptake and use in population that need it most.

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Thank you

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