

Rabies vaccines and immunoglobulins: WHO position April 2018

The April 2018 position paper replaces the 2010 WHO position on rabies vaccines. It presents new evidence in the field of rabies and the use of rabies vaccines, focussing on programmatic feasibility, simplification of vaccination schedules and improved cost-effectiveness.

The recommendations concern the two main immunization strategies, namely vaccination for post-exposure prophylaxis (PEP) and vaccination for pre-exposure prophylaxis (PrEP). 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

Background

Rabies is a viral zoonotic disease responsible for an estimated 59 000 human deaths and over 3.7 million disability-adjusted life years (DALYs) lost every year.² Rabies is almost invariably fatal once clinical signs occur, as a result of acute progressive encephalitis. Rabies occurs mainly in underserved populations, both rural and urban.³ Most cases occur in Africa and Asia, with approximately 40% of cases in children aged <15 years. Mass vaccination campaigns targeting dogs is the principal strategy for rabies control by interrupting rabies virus (RABV) transmission between dogs and reducing transmission to humans and other mammals. Human-to-human transmission of rabies has never been confirmed, except extremely rarely as a result of infected tissue and organ transplantation.^{4,5} The primary diagnosis of rabies relies on clinical presentation and history of exposure to a suspect rabid animal or RABV.

Rabies vaccines can be administered by two different routes, intradermal (ID) or intramuscular (IM), and according to different schedules.

WHO Position

Administration of rabies vaccines:

For both PEP and PrEP, vaccines can be administered by either the ID or IM route. For all age groups ID injection sites are the deltoid region and either the anterolateral thigh or suprascapular regions. The recommended site for IM administration is the deltoid area of the arm for adults and children aged ≥ 2 years, and the anterolateral area of the thigh for children aged <2 years. Rabies vaccine should not be administered IM in the gluteal area. One ID dose is 0.1 mL of vaccine and one IM dose is an entire vial of vaccine, irrespective of the vial size.

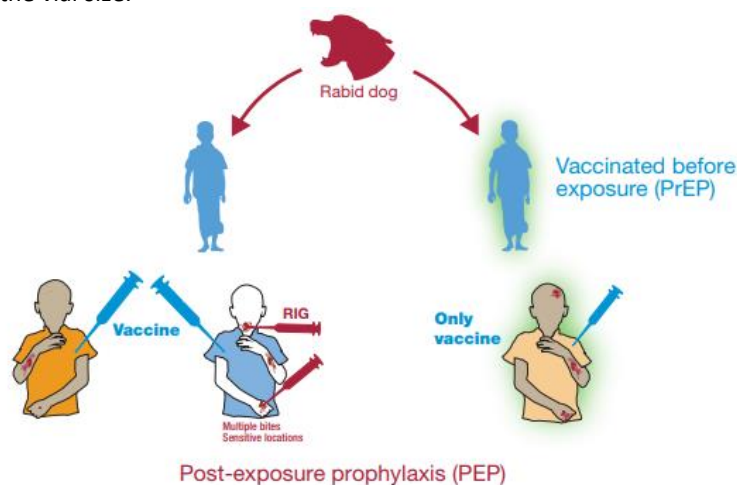


Figure 1: WHO recommends 2 main immunization strategies for the prevention of human rabies: Post-exposure prophylaxis (PEP) and Pre-exposure prophylaxis (PrEP)

Post-exposure prophylaxis (PEP)

PEP consists of the following steps:

1. All bite wounds, scratches and RABV-exposure sites 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

¹ <http://apps.who.int/iris/bitstream/10665/259533/1/WER9248.pdf?ua=1>

² Hampson K. et al. Estimating the Global Burden of Endemic Canine Rabies. *Trop Dis.* 2015; 9 (5):e0003786.

³ Tarantola A. Four Thousand Years of Concepts Relating to Rabies in Animals and Humans, Its Prevention and Its Cure. *Trop Med Infect Dis.* 2017; 2, 5.

⁴ Rupprecht CE et al. Current Status and Development of Vaccines and Other Biologics for Human Rabies Prevention. *Expert Rev Vaccines.* 2016 Jun;15(6):731-49.

⁵ WHO Expert Consultation on Rabies, third report: WHO Technical Series Report, Geneva 2018 (in press) ISBN 978-92-4-121021-8

amounts of water, is required. Where available, an iodine-containing, or similarly viricidal, topical preparation should be applied to the wound.

2. A series of rabies vaccine injections should be administered promptly after an exposure.
3. 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.

WHO recommends PEP for category II and III exposures (see Table 1).

The WHO rabies exposure categories are:

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).

ID PEP schedules are cost- and dose-sparing and cost-effectiveness increases with numbers of patients seen in clinics.

If a repeat exposure occurs within 3 months of completion of PEP, only wound treatment is required, neither vaccine nor RIG are needed.

Table 1: PEP recommendations by category of exposure

	Category I exposure	Category II exposure	Category III exposure
Immunologically naive individuals of all age groups	Wash exposed skin surfaces. No PEP required.	Wound washing and immediate vaccination:	Wound washing and immediate vaccination
		- 2-sites ID on days 0, 3 and 7 ⁶ OR	- 2-sites ID on days 0, 3 and 7 ⁶ OR
		- 1-site IM on days 0, 3, 7 and between day 14-28 ⁷ OR	- 1-site IM on days 0, 3, 7 and between day 14-28 ⁷ OR
Previously immunized individuals of all age groups	Wash exposed skin surfaces No PEP required.	- 2-sites IM on days 0 and 1-site IM on days 7, 21 ⁸ RIG is not indicated.	- 2-sites IM on days 0 and 1-site IM on days 7, 21 ⁸ RIG administration is recommended.
		Wound washing and immediate vaccination*:	Wound washing and immediate vaccination*:
		- 1-site ID on days 0 and 3; OR	- 1-site ID on days 0 and 3; OR
		- at 4-sites ID on day 0; OR	- at 4-sites ID on day 0; OR
		- at 1-site IM on days 0 and 3); RIG is not indicated.	- at 1-site IM on days 0 and 3; RIG is not indicated.

* *except if complete PEP already received within <3 months previously*

Changes in rabies vaccine product and/or the route of administration during the same PEP course are acceptable, if unavoidable, to ensure PEP course completion. Should a vaccine dose be delayed for any reason, the PEP schedule should be resumed (not restarted). Individuals with documented immunodeficiency should be evaluated on a case-by-case basis and receive a complete course of ID or IM PEP, including RIG.

Rabies immunoglobulin administration

RIG provides passive immunization and is administered only once, as soon as possible after the initiation of PEP and not beyond day 7 after the first dose of vaccine. Correctly administered, RIG neutralizes the virus at the wound site within a few hours. eRIG is less costly than hRIG, both have shown similar clinical outcomes in preventing rabies. As eRIG products are now highly purified, skin testing before administration is unnecessary and should be abandoned.

To confer the maximum public health benefit, WHO recommends the following:

- The maximum dose is 20 IU (hRIG) and 40 IU (eRIG) per kg body weight. There is no minimum dose.
- Infiltrate as much as possible into the wound; the remainder of the calculated dose of RIG does not need to be injected IM at a distance from the wound but can be fractionated in smaller, individual syringes to be used for other patients, aseptic retention given.

If RIG is not available, thorough, prompt wound washing, together with immediate administration of the first vaccine dose, followed by a complete course of rabies vaccine, is highly effective in preventing rabies. Vaccines should never be withheld, regardless of the availability of RIG.

⁶ one-week, 2-site ID regimen / Institut Pasteur du Cambodge (IPC) regimen/2-2-2-0-0; Duration of entire PEP course: 7 days.

⁷ two week IM PEP regimen/4-dose Essen regimen/1-1-1-1-0; Duration of entire PEP course: between 14 to 28 days.

⁸ three week IM PEP regimen/Zagreb regimen/2-0-1-0-1; Duration of entire PEP course: 21 days.

If a limited amount of RIG is available, RIG allocation should be prioritized for exposed patients based on the following criteria: Multiple bites, deep wounds, bites to highly innervated parts of the body (such as head, neck and hands), severe immunodeficiency, the biting animal is a confirmed or probable rabies case, and bites, scratches or exposures of mucous membranes caused by a bat.

Pre-exposure prophylaxis (PrEP)

Pre-exposure prophylaxis (PrEP) is the administration of several doses of rabies vaccine before exposure to RABV. PrEP is recommended for individuals at higher risk due to occupation. PrEP should be considered in sub-populations living in remote, rabies endemic areas, where access to PEP is difficult, the dog bite incidence is >5% per year or vampire bat rabies is known to be present.

The immune response to subsequent rabies vaccine boosters such as PEP when exposed, can be recalled very effectively even decades after PrEP.

For immunologically naive individuals of all age groups WHO recommends the following PrEP schedules: a 2 sites ID or a 1-site IM vaccine administration on days 0 and 7.

A routine PrEP booster or serology for neutralizing antibody titres is recommended only if a continued, high risk of rabies exposure remains.

Individuals with documented immunodeficiency should be evaluated on a case-by-case basis and best receive an ID or IM PrEP schedule as above, plus a third vaccine administration between days 21 to 28. Additionally, in the event of an exposure, a complete PEP course, including RIG, is recommended.