

# Frequently asked questions about rabies for Clinicians



## SECTION II. TABLE OF CONTENTS

<b>GLOBAL BURDEN OF RABIES</b>	<b>4</b>
Q.1 WHAT IS THE GLOBAL BURDEN OF RABIES?	4
<b>FOLLOWING EXPOSURE: POST-EXPOSURE (PEP) INDICATIONS AND USE</b>	<b>6</b>
Q.2 HOW DOES ONE TREAT A PERSON WITH AN ANIMAL BITE?	6
Q.3 WHAT ARE THE WHO RABIES EXPOSURE CATEGORIES	6
Q.4 WHAT ARE ATYPICAL EXPOSURES AND WHICH INDIVIDUALS REQUIRE PEP?	6
Q.5 WHAT ARE THE MAIN FEATURES OF PEP?	7
<b>VACCINATION SCHEDULES</b>	<b>8</b>
Q.6 WHAT IS THE STANDARD VACCINATION SCHEDULE FOR RABIES PROPHYLAXIS?	8
Q.6 A) POST-EXPOSURE PROPHYLAXIS (PEP)	8
Q.6 B) PRE-EXPOSURE PROPHYLAXIS (PREP)	9
Q.7 WHEN ARE BOOSTER VACCINATIONS RECOMMENDED?	10
Q.8 ARE THERE ANY SHORTER PREP REGIMENS?	10
Q.9 IF A PREVIOUSLY IMMUNIZED PERSON IS BITTEN BY A RABID DOG AGAIN, WHAT IS THE RE-EXPOSURE VACCINATION SCHEDULE?	10
Q.10 IS IT NECESSARY TO PERFORM AN ANTIBODY TEST ON THE PATIENT FOLLOWING ANTI-RABIES VACCINATION?	11
Q.11 IS IT ACCEPTABLE TO CHANGE THE VACCINE BRAND OR MANUFACTURER DURING PEP OR PREP?	11
Q.12 IS IT ACCEPTABLE TO CHANGE THE ROUTE OF ADMINISTRATION DURING PEP OR PREP?	11
<b>RABIES VACCINE SAFETY</b>	<b>12</b>
Q.13 CAN RABIES VACCINES AND IMMUNOGLOBULINS BE GIVEN TO A PREGNANT WOMAN OR A LACTATING MOTHER?	12
Q.14 HOW DO I MANAGE A PATIENT WHO IS IMMUNOCOMPROMISED?	12
Q.15 ARE THERE ANY CONTRAINDICATED MEDICINES OR DIETARY RESTRICTIONS DURING ANTI-RABIES VACCINATION?	12
Q.16 ARE THERE ANY ADVERSE EFFECTS OF RABIES VACCINATION?	12
Q.17 IS THERE ANY POSSIBILITY OF VACCINE FAILURE AFTER PEP?	13
<b>RABIES VACCINE</b>	<b>13</b>
Q.18 WHAT IS RABIES VACCINE?	13
Q.19 WHAT TYPES OF RABIES VACCINES ARE USED?	13
Q.20 WHAT RABIES VACCINES ARE RECOMMENDED BY WHO?	14
Q.21 HOW SHOULD ANTI-RABIES VACCINES BE STORED TO MAINTAIN THEIR SAFETY AND POTENCY BEFORE ADMINISTRATION?	14
Q.22 WHAT ARE THE IMPORTANT POINTS TO CONSIDER WHILE ADMINISTERING RABIES VACCINE?	14
<b>INTRADERMAL VACCINATION</b>	<b>16</b>
Q.23 DO WE NEED TO CONSIDER SPECIFIC VACCINE POTENCY FOR INTRADERMAL VACCINATION?	16

**Q.24 HOW DOES INTRADERMAL RABIES VACCINATION WORK WHEN THE DOSE IS SO SMALL? DOES IT FULLY PROTECT AGAINST RABIES EXPOSURE? 16**

**RABIES IMMUNOGLOBULIN 16**

**Q.25 WHAT IS RABIES IMMUNOGLOBULIN (RIG) AND HOW IS IT USED? 16**

**Q.26 PRIORITIZATION OF RIG ALLOCATION 17**

**Q.27 IS IT NECESSARY TO PERFORM A SKIN SENSITIVITY TEST WHILE USING ERIG? 18**

**Q.28 WHAT PRECAUTIONS SHOULD BE TAKEN WHILE ADMINISTERING RIG? 18**

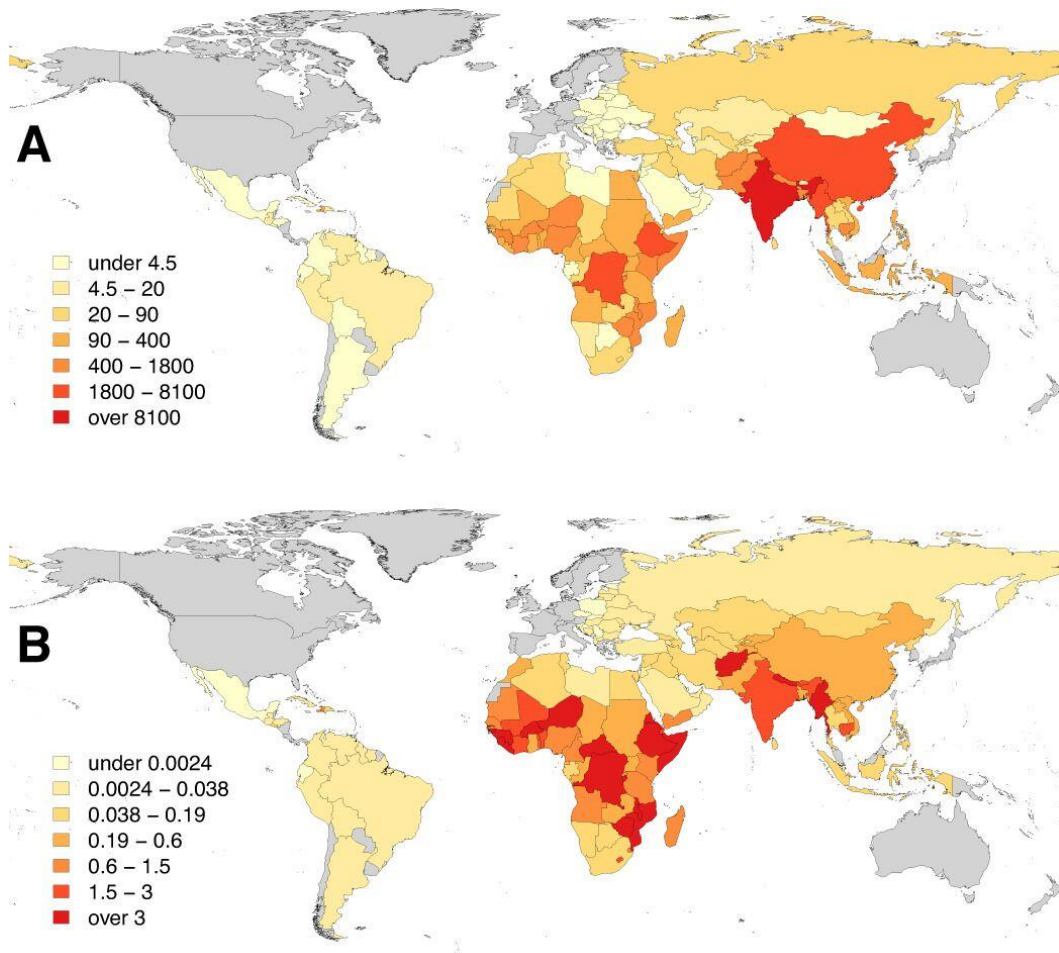
**MANAGEMENT OF CLINICALLY AFFECTED PATIENTS 18**

**Q.29 WHAT PALLIATIVE CARE IS AVAILABLE FOR RABIES PATIENTS? 18**

## GLOBAL BURDEN OF RABIES

### Q.1 WHAT IS THE GLOBAL BURDEN OF RABIES?

Every year, an estimated 60 000 people die of rabies, one of the oldest and most terrifying diseases known to man (Figure 1).



**Figure 1. Global burden of dog-transmitted human rabies and distribution of A) human rabies deaths and B) per capita death rates (per 100 000 persons)**

Source: Hampson K, Coudeville L, Lembo T, Sambo M, Kieffer A, Attlan M et al. Estimating the global burden of endemic canine rabies. *PLoS Negl Trop Dis.* 2015;9:e0003709. doi:10.1371/journal.pntd.0003709.

Human deaths from rabies are significantly underreported in many parts of the world. Standardized metrics such as the disability-adjusted life year (DALY) incorporate premature mortality and disability due to disease. As rabies is rapidly fatal, disability accounts for a minimal part of the disease burden. In the few places where they remain in use, nerve tissue vaccines contribute to vaccine failure and cause severe side-effects lasting 4–7 months.

The most recent and comprehensive burden study includes an estimate of the economic burden of rabies, which includes productivity losses due to mortality or morbidity, direct costs such as the cost of rabies vaccines and

immunoglobulins, and indirect costs such as transport and income losses incurred by patients. Livestock losses, and the cost of surveillance and preventative measures such as dog vaccination were also included.

*Rabies is a neglected disease.* In places where there are no organized control activities or surveillance, data are weak. Poor surveillance, underreporting, frequent misdiagnosis of rabies and an absence of coordination among all the sectors involved have led to an underestimation of the scale of the disease burden. As a result, modelling approaches have been adopted, using data from country clusters to extrapolate estimates where specific data are lacking. Improving surveillance and strengthening regional and global reporting systems would increase the accuracy of burden estimates, and the needs and impacts of control programmes. Country-specific burden studies and improved surveillance are encouraged to obtain more reliable global estimates.

In 2017, WHO issued a call inviting countries to participate in the collection of global rabies data:

[http://www.who.int/rabies/advancing\\_global\\_rabies\\_data\\_collection/en/](http://www.who.int/rabies/advancing_global_rabies_data_collection/en/)

Rabies occurs worldwide and on all continents except for Antarctica. However, the vast majority of human deaths (up to 99%) are caused by the classical rabies virus transmitted by dogs (Fig. 2). Anyone bitten by a rabid animal or exposed to the saliva of a rabid animal is at risk from developing rabies and should seek immediate medical advice to initiate life-saving post-exposure prophylaxis.

Rabies kills about 60 000 people each year, mostly in Asia and Africa. Children are at higher risk of rabies because they often play with animals; are more likely to receive a bite to the face or neck; and may not report bites or scratches received during play.

Bites from rabid dogs cause up to 99% of human rabies cases. Rabies is almost always fatal once clinical signs occur. There is currently no effective treatment for rabies after clinical signs appear. However, the disease is preventable through vaccination either before or immediately after an exposure.

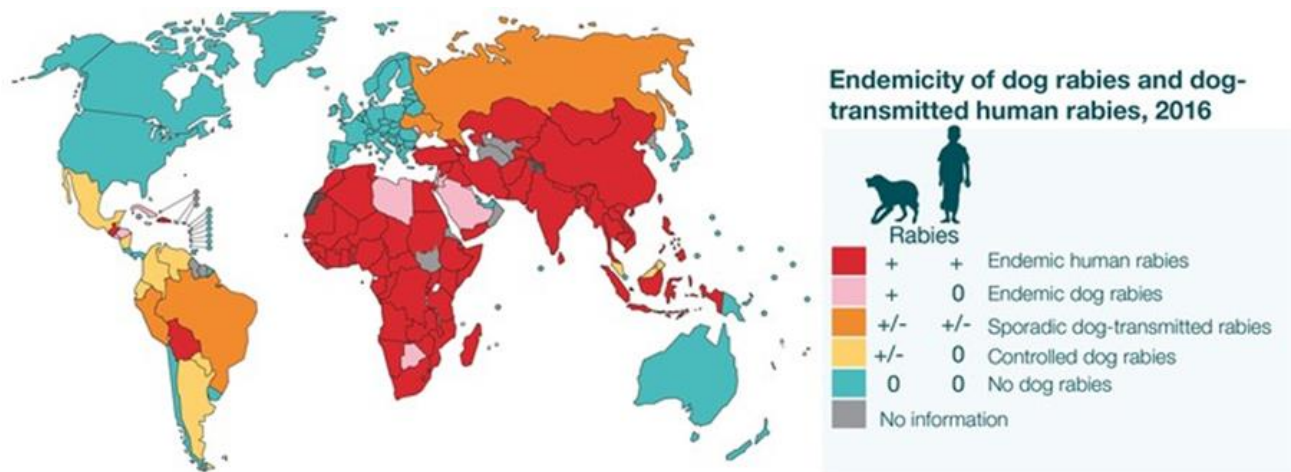


Figure 2. Distribution of dog-mediated rabies worldwide, based on 2016 data

## FOLLOWING EXPOSURE: POST-EXPOSURE (PEP) INDICATIONS AND USE

### Q.2 HOW DOES ONE TREAT A PERSON WITH AN ANIMAL BITE?

- Wounds should be immediately washed and flushed for about 15 minutes, with soap or detergent and copious amounts of water of all bite wounds and scratches. If soap is not available, flush with water alone. *This is the most effective first-aid treatment against rabies.*
- Where available, an iodine-containing, or similarly viricidal, topical preparation should be applied to the wound.
- Assess the person's vaccination status, e.g. whether diphtheria, pertussis, tetanus (DPT) or tetanus toxoid vaccination has been given in the past. A tetanus toxoid vaccine should be administered when necessary.
- Antimicrobials can be prescribed if complication from bacterial infection is suspected.
- Analgesics can be used.

AVOID covering the wound with dressings or bandages.

DO NOT suture the wound.

- If necessary for closing large wounds, **suturing should be done after infiltration of the wound with rabies immunoglobulin (RIG).**
- The sutures should be loose and not interfere with free bleeding and drainage. It is well established that secondary suture of bite wounds results in better cosmetic outcomes.

### Q.3 WHAT ARE THE WHO RABIES EXPOSURE CATEGORIES?

#### RABIES EXPOSURE CATEGORIES AS DEFINED BY WHO

<i>Category I</i> (no exposure)	<ul style="list-style-type: none"><li>• Touching or feeding animals</li><li>• Licks on intact skin</li></ul>
<i>Category II</i> (exposure)	<ul style="list-style-type: none"><li>• Nibbling of uncovered skin</li><li>• Minor scratches or abrasions without bleeding</li></ul>
<i>Category III (severe exposure)</i>	<ul style="list-style-type: none"><li>• Single or multiple transdermal bites or scratches</li><li>• Contamination of mucous membrane with saliva from licks</li><li>• Licks on broken skin</li><li>• Exposures due to direct contact with bats</li></ul>

### Q.4 WHAT ARE ATYPICAL EXPOSURES AND WHICH INDIVIDUALS REQUIRE PEP?

Human-to-human transmission of rabies has not been confirmed, except in the case of transplants and a single case of probable perinatal transmission. Rabies virus can, however, be found in saliva, tears and nervous tissues of people with rabies, which represents a theoretical route of transmission. Rabies virus has also been transmitted through ingestion of experimentally infected animals.

For further information on atypical exposure routes, refer to section 8.3.2 of the WHO Expert Consultation on Rabies (3<sup>rd</sup> report): [http://www.who.int/rabies/resources/who\\_trs\\_1012/en/](http://www.who.int/rabies/resources/who_trs_1012/en/).

#### ATYPICAL EXPOSURES AND PEP ADMINISTRATION

<i>PEP indicated</i>	<ul style="list-style-type: none"><li>• Organ transplant recipients from rabies-infected organ donors</li><li>• Bites from, or mucosal exposure (e.g. medical procedures, kissing, intimate touching) to a rabies-infected person</li><li>• Individuals with exposures to rabies-infected animals during butchering or processing (eating meat from rabid animals is NOT advised)</li><li>• Healthcare workers or caregivers of rabies patients who were exposed to saliva, tears, urine or nervous tissues of the patient</li><li>• Individuals co-exposed to an animal which caused a rabies case</li><li>• Persons inhaling air in caves with a high density of bats</li></ul>
<i>PEP not indicated</i>	<ul style="list-style-type: none"><li>• Individuals bitten by rodents (unless the rodent shows signs or tests positive for rabies)</li><li>• Drinking milk, including breastmilk, from a rabies-infected person or animal is NOT advised. However, there is no evidence that consuming milk, including breastmilk, could transmit rabies.</li></ul>

#### Q.5 WHAT ARE THE MAIN FEATURES OF PEP?

PEP is the administration of wound care and immunization after a potential exposure to the rabies virus.

PEP **always** includes:

1. Thorough washing and flushing of the wound for approximately 15 minutes, with soap or detergent and copious amounts of water.
2. Where available, an iodine-containing, or similarly viricidal, topical preparation applied to the wound.
3. A series of rabies vaccine injections administered **immediately** after an exposure.

PEP **sometimes** includes:

4. Administration of rabies immunoglobulins (RIG) in severe category III exposures

Further information can be found in the 2018 WHO rabies position paper

([http://www.who.int/rabies/resources/who\\_wer9316/en/](http://www.who.int/rabies/resources/who_wer9316/en/))

## VACCINATION SCHEDULES

### Q.6 WHAT IS THE STANDARD VACCINATION SCHEDULE FOR RABIES PROPHYLAXIS?

#### Q.6 A) POST-EXPOSURE PROPHYLAXIS (PEP)

##### RECOMMENDED PEP ACCORDING TO TYPE OF EXPOSURE

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

<sup>1</sup> One-week, 2-site ID regimen / Institut Pasteur du Cambodge (IPC) regimen/2-2-2-0-0; duration of entire PEP course: 7 days.

<sup>2</sup> Two-week IM PEP regimen/4-dose Essen regimen/1-1-1-1-0; duration of entire PEP course: between 14 and 28 days.

<sup>3</sup> Three-week IM PEP regimen/Zagreb regimen/2-0-1-0-1; duration of entire PEP course: 21 days.

<sup>4</sup> Immediate vaccination is not recommended if complete PEP already received within <3 months previously

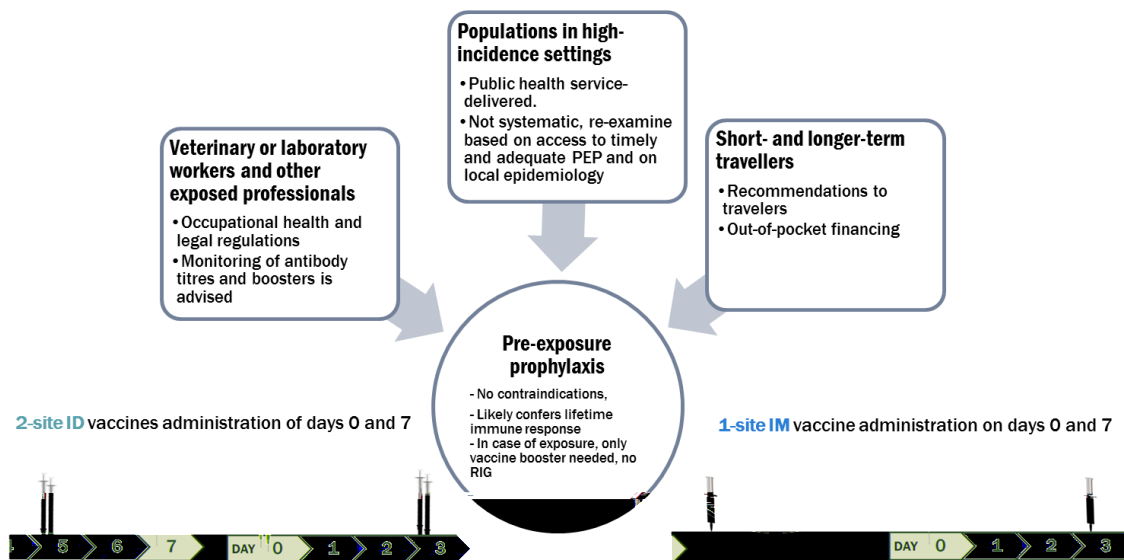


WHO-RECOMMENDED AND ALTERNATIVE PEP PROPHYLACTIC REGIMENS

PEP regimens	Duration of course	No. of injection sites per clinic visit (days 0, 3, 7, 14, 21–28)
<b>Immunologically naïve (1<sup>st</sup> time PEP)</b>		
<i>WHO-recommended intradermal regimen</i>		
1 week, two sites	7 days	2-2-2-0-0
<i>WHO-recommended intramuscular regimen</i>		
2 weeks	14–28 days	1-1-1-1-0
3 weeks	21 days	2-0-1-0-1
<b>Previously immunized</b>		
<i>WHO-recommended intradermal regimen</i>		
1-site	3 days	1-1-0-0-0
4-sites	1 day	4-0-0-0-0
<i>WHO-recommended intramuscular regimen</i>		
1 week, four sites	3 days	1-1-0-0-0

Q.6 B) PRE-EXPOSURE PROPHYLAXIS (PREP)

# Pre-exposure prophylaxis



An additional visit may be clinically considered in case of immunodeficiency or chloroquine-related drugs

## WHO-RECOMMENDED AND ALTERNATIVE PREP PROPHYLACTIC REGIMENS

PrEP regimens	Duration of course	No. of injection sites per clinic visit (days 0, 3, 7, 14, 21–28)
<i>WHO-recommended intradermal regimen</i>		
Two visits	7 days	2-0-2-0-0
<i>WHO-recommended intramuscular regimen</i>		
Two visits	7 days	1-0-1-0-0
<i>PrEP under specific circumstances</i>		
Single visit, intradermal	1 day	2-0-0-0-0
Single visit, intramuscular	1 day	1-0-0-0-0

### Q.7 WHEN ARE BOOSTER VACCINATIONS RECOMMENDED?

Routine PrEP booster vaccinations are recommended only for individuals working in laboratories or manufacturing plants with high concentrations of live rabies viruses. Antibody testing for these professionals should be done at intervals of 1–2 years. All other individuals at continued risk of exposure to rabies virus should be evaluated on a case-by-case basis for scheduling of antibody titre monitoring, if available, or a routine booster. Routine booster vaccination is recommended if the antibody titre is < 0.5 IU/ml.

A routine pre-exposure booster vaccination, if indicated, consists of:

**1-site ID (intradermal) or 1-site IM (intramuscular) vaccine administration**

If available, antibody titre monitoring is preferred to the routine administration of boosters.

Further information can be found in the 2018 WHO rabies position paper ([http://www.who.int/rabies/resources/who\\_wer9316/en/](http://www.who.int/rabies/resources/who_wer9316/en/))

### Q.8 ARE THERE ANY SHORTER PREP REGIMENS?

When there are time constraints or a single visit to the clinic is the only option, a shortened PrEP course can be given i.e. *a 2-site ID or a 1-site IM injection on Day 0*.

The patient should plan to **receive a second vaccination as soon as possible** to complete the PrEP. However, in healthy individuals this regimen can provide protection for up to 1 year from the date of vaccination.

In the case of a rabies exposure before the second vaccination, the patient is recommended to receive a full course of PEP, with RIG in cases of severe exposure.

### Q.9 IF A PREVIOUSLY IMMUNIZED PERSON IS BITTEN BY A RABID DOG AGAIN, WHAT IS THE RE-EXPOSURE VACCINATION SCHEDULE?

If a previously immunized person is bitten by a rabid dog within 3 months of completing a full course of PEP or PrEP, **no new course** of PEP is required.

For exposures occurring more than 3 months after a PEP or PrEP course, treat as PEP for previously immunized individuals; 1 site ID or IM vaccination at days 0 and 3, or a 4-site ID accelerated vaccination on day 0. *RIG is not indicated.*

#### Q.10 IS IT NECESSARY TO PERFORM AN ANTIBODY TEST ON THE PATIENT FOLLOWING ANTI-RABIES VACCINATION?

No. It is not necessary on a routine basis when human rabies vaccines are properly stored and given according to the approved schedule in a healthy individual. An effective recall of anti-rabies immune response is possible over decades, even in the absence of detectable titres.

Antibody testing is recommended only under special medical conditions, such as for immunocompromised patients to check whether seroconversion happened or antibody titres are at satisfactory levels.

#### Q.11 IS IT ACCEPTABLE TO CHANGE THE VACCINE BRAND OR MANUFACTURER DURING PEP OR PREP?

A change in the vaccine product (brand or manufacturer) during a PEP or PrEP course is acceptable if such a change is unavoidable. Restarting the series of injections is not necessary; vaccination should continue according to the previous schedule.

*Examples of when such changes in PEP or PrEP regimens might occur:*

The patient receives the first vaccination at a bite centre away from their home. Upon returning home the patient receives the remaining series of vaccines at their local clinic.

#### Q.12 IS IT ACCEPTABLE TO CHANGE THE ROUTE OF ADMINISTRATION DURING PEP OR PREP?

A change in the route of administration during a PEP or PrEP course is acceptable if such a change is unavoidable. Restarting the series of injections is not necessary; vaccination should continue according to the schedule for the new route of administration.

*When might such changes in a PEP or PrEP regimen occur?*

- The patient receives the first vaccine administration in a small clinic in a rural area (likely IM), but receives the remainder of the schedule in a larger clinic (likely ID).
- A traveller receives the first booster abroad, and the remainder of the PEP course at home.
- Hospital protocol dictates that rabies vaccines should be given IM. Due to shortage in vaccine and high demand for PEP, patients who return to receive subsequent vaccines are given rabies vaccines ID.

## RABIES VACCINE SAFETY

### Q.13 CAN RABIES VACCINES AND IMMUNOGLOBULINS BE GIVEN TO A PREGNANT WOMAN OR A LACTATING MOTHER?

Rabies vaccines and RIG are safe and efficacious during pregnancy. Life-saving PEP should never be withheld from pregnant and lactating women. Any of the WHO-recommended PEP regimens can be used.

*Pregnancy and lactation are never contraindications for receiving rabies post-exposure prophylaxis.*

### Q.14 HOW DO I MANAGE A PATIENT WHO IS IMMUNOCOMPROMISED?

For immunocompromised individuals, who are not clinically monitored or well-managed, with a WHO category II and III rabies exposure the following is recommended:

1. **Thorough washing and antiseptics of the wound.**
2. A full course of PEP vaccination, either ID or IM, with RIG is indicated (even if previously immunized through PEP or PrEP).
3. Serology to test antibody titres 2–4 weeks after the first vaccine administration can support the decision whether an additional dose of vaccine is required, if the immune response of the individual is inadequate.
4. Consultation with an infectious disease specialist is advised.

*Individuals who are clinically monitored and well-managed, such as HIV-infected individuals under antiretroviral therapy, are not considered immunocompromised and have shown to respond comparably to rabies and other vaccinations as healthy individuals.*

### Q.15 ARE THERE ANY CONTRAINDICATED MEDICINES OR DIETARY RESTRICTIONS DURING ANTI-RABIES VACCINATION?

No. There is no scientific evidence to support any dietary restrictions during PEP or PrEP. In general, rabies vaccines are safe and efficacious to give with most other medications. However, if the patient is currently taking any immunosuppressant medicines it is best to consult an infectious disease specialist regarding appropriate treatment options.

Individuals under treatment with chloroquine or hydroxychloroquine should receive standard PrEP or PEP (ID or IM). Out of caution and where feasible, PrEP should be completed before chloroquine or hydroxychloroquine treatment is initiated.

### Q.16 ARE THERE ANY ADVERSE EFFECTS OF RABIES VACCINATION?

Rabies vaccines have been shown to be safe and well tolerated. Adverse events may occur, however, depending in part on the purity of the inactivated rabies virus, which may vary among batches.

In 35–45% of vaccinated people, minor, transient erythema, pain or swelling occurs at the site of injection, particularly after intradermal administration of a booster. Mild systemic adverse events, such as transient fever, headache, dizziness and gastrointestinal symptoms, have been observed in 5–15% of vaccinated people.

Serious adverse events are rare and include allergic reactions.

All patients should be told about the possible adverse effects of rabies vaccination, but they must be advised that it is essential to continue vaccination – even if there are local or mild systemic adverse reactions. *Healthcare professionals should always be prepared to intervene in the case of a severe adverse vaccine reaction.*

#### Q.17 IS THERE ANY POSSIBILITY OF VACCINE FAILURE AFTER PEP?

Rabies vaccines are safe and highly efficacious, and true rabies vaccine failures are extremely rare if high-quality vaccines are used. There are occasional reports of human rabies deaths in patients who received PEP, however these were mostly due to inappropriate, incomplete or ineffective administration of PEP and individual health status.

Investigations of deaths due to rabies in patients who received PEP revealed that delay in seeking treatment, improper wound care, unnoticed wounds and lack of patient compliance to vaccination schedules, among other factors (e.g. quality of vaccine and cold chain), were the main reasons for treatment failure and subsequent death.

An additional cause for vaccine failure results from inoculation of the virus directly into the nerve, whereby the virus avoids recourse by the immune system and the effects of the rabies vaccines. These patients may benefit from receiving RIG.

### RABIES VACCINE

#### Q.18 WHAT IS RABIES VACCINE?

Since their development more than four decades ago, concentrated, purified cell culture and embryonated egg-based rabies vaccines – jointly referred to as CCEEVs – have proved to be safe and effective in preventing rabies. These vaccines are intended for both pre-exposure and post-exposure prophylaxis and have been administered to millions of people worldwide. Prompt administration of vaccine after exposure combined with proper wound management and, when indicated, administration of rabies immunoglobulins, is almost invariably effective in preventing rabies, even after a severe exposure.

The latest (2018) information on rabies vaccines and immunoglobulins is available from the WHO position paper ([http://www.who.int/rabies/resources/who\\_wer9316/en/](http://www.who.int/rabies/resources/who_wer9316/en/)).

#### Q.19 WHAT TYPES OF RABIES VACCINES ARE USED?

The rabies vaccines in use can be categorized based on their origin, namely tissue culture origin or embryonated egg origin.

Modern human rabies vaccines are commercially available as cell cultured vaccine (CCV), including purified chicken embryo vaccine (PCECV), purified vero cell rabies vaccine (PVRV), human diploid cell vaccine (PVRV) and purified duck embryo vaccine (PDEV).

WHO encourages the use of a cost-effective intradermal rabies vaccination schedule, even when off-label, because it is safe and efficacious, to improve accessibility, affordability and availability of modern rabies vaccines.

Since 1984, WHO has strongly *recommended discontinuation of the production and use of nerve tissue vaccines* and their replacement by modern cell culture or embryonated egg vaccines. Nerve tissue vaccines induce severe adverse reactions more frequently and are less immunogenic than CCEEVs.

#### Q.20 WHAT RABIES VACCINES ARE RECOMMENDED BY WHO?

WHO maintains a list of rabies vaccines that have been WHO-prequalified and are commercially available on the international market. The list is available online ([https://extranet.who.int/gavi/PQ\\_Web/](https://extranet.who.int/gavi/PQ_Web/)). If no prequalified rabies vaccines are available, WHO recommends using a rabies vaccine provided by a manufacturer who maintains other vaccines prequalified with WHO (i.e. vaccine manufacturers with prequalification for other diseases).

WHO encourages pharmaceutical companies to adhere to the WHO prequalification procedure to ensure good manufacturing practices and quality assurance for countries.

Vaccines supplied through United Nations agencies are in general prequalified by WHO.

#### Q.21 HOW SHOULD ANTI-RABIES VACCINES BE STORED TO MAINTAIN THEIR SAFETY AND POTENCY BEFORE ADMINISTRATION?

After growth in cell culture (or embryonic egg), rabies vaccines are concentrated, purified, inactivated and lyophilized to extend their shelf-life and stability.

Human rabies vaccines are not supplied in multi-dose vials for intramuscular injection, and usually do not contain preservatives.

The shelf-life of these vaccines is indicated by the manufacturer on the package insert, generally  $\geq 3$  years, provided they are stored at 2–8 °C and protected from sunlight.

After reconstitution with sterile diluent, the vaccines should be used immediately or within 6 h if kept at between 2 °C and 8 °C, as partially used vials of rabies vaccine may become contaminated.

Further information can be found in the 2018 WHO rabies position paper ([http://www.who.int/rabies/resources/who\\_wer9316/en/](http://www.who.int/rabies/resources/who_wer9316/en/))

---

**Storage:** 2–8 °C, protect from sunlight

**Shelf-life:**  $\geq 3$  years; 6 h if reconstituted and stored at 2–8°C

#### Q.22 WHAT ARE THE IMPORTANT POINTS TO CONSIDER WHILE ADMINISTERING RABIES VACCINE?

WHO strongly advocates the use of dose- and cost-sparing administration of ID rabies vaccines, even when used off-label. Irrespective of the size of the vaccine vial, an ID volume per dose is 0.1 ml. Opened vials should be used within 6 hours.

When administering rabies vaccine IM, the entire vaccine vial should be used.

All rabies vaccines are available as single-dose vials for IM use and should be injected into the deltoid region (i.e. upper arm, near the shoulder) or, in small children, into the anterolateral area of the thigh muscle (on the upper thigh).

As with other injections, the rabies vaccine should NOT be given in the gluteal region (buttocks) because of low absorption due to the presence of adipose (fat) tissue.

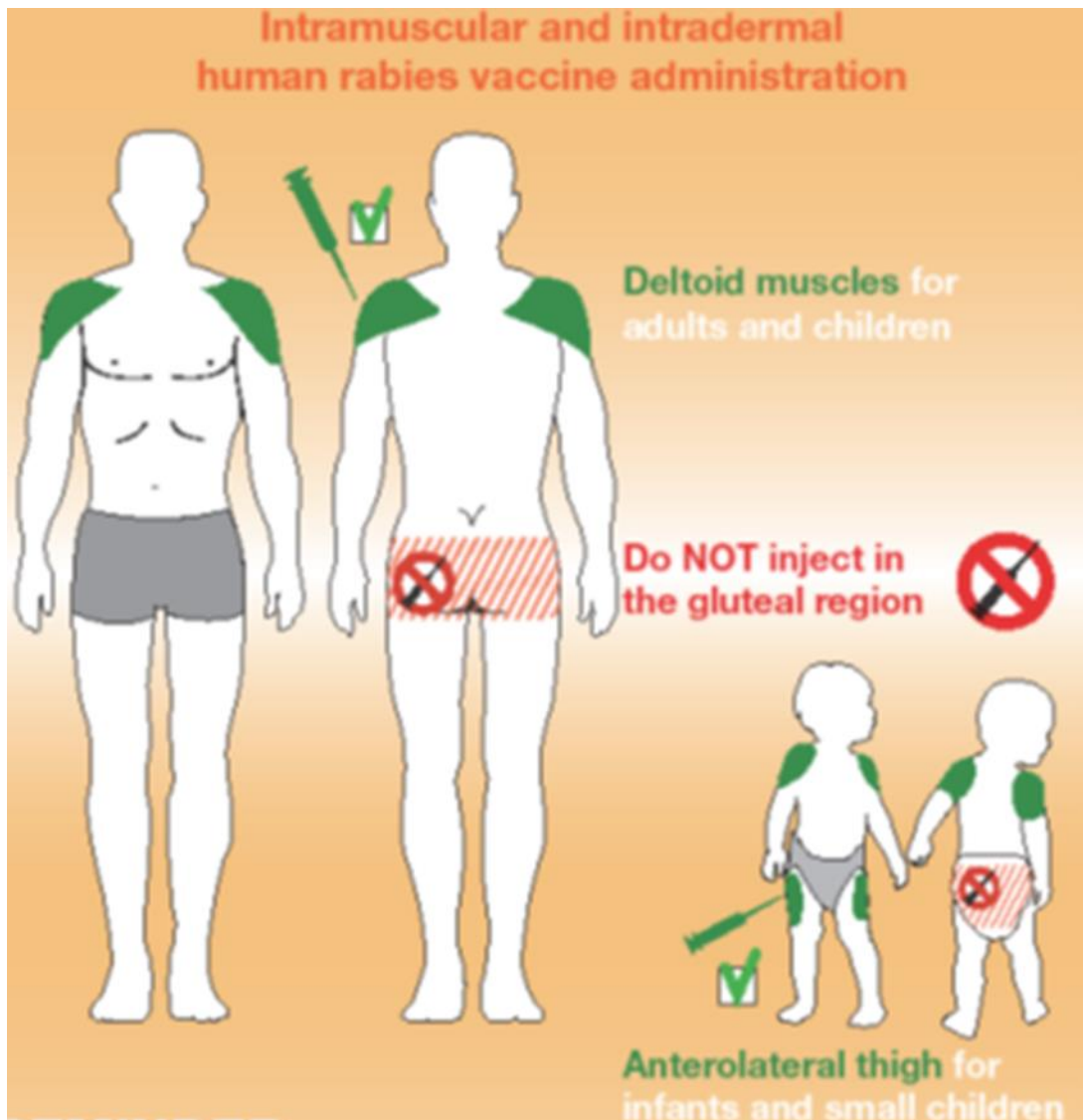


Figure 3. Sites for intramuscular and intradermal administration of human rabies vaccine (WHO Expert Consultation on Rabies Third Report, 2018)

## INTRADERMAL VACCINATION

### Q.23 DO WE NEED TO CONSIDER SPECIFIC VACCINE POTENCY FOR INTRADERMAL VACCINATION?

No. There has been concern as single IM doses are reconstituted in different volumes depending on manufacturers. The WHO-recommended minimum potency is 2.5 IU per IM dose and the WHO-recommended volume of a single dose of rabies vaccine administered per ID site is 0.1 ml, regardless of vaccine vial size.

### Q.24 HOW DOES INTRADERMAL RABIES VACCINATION WORK WHEN THE DOSE IS SO SMALL? DOES IT FULLY PROTECT AGAINST RABIES EXPOSURE?

Intradermal vaccination is a multi-site (upper arms, lateral thighs, suprascapular) vaccination technique that elicits a prompt and highly protective immune response with a small dose.

In the past, eight-site and four-site ID administration schedules were standard. However, clinical trials and immunological studies clearly demonstrate that *two-site ID administration is efficacious, user-friendly and cost-effective.*



The immune responses induced by ID and IM regimens are comparable, although the immune response pathways are slightly different. In ID vaccination, rabies antigen is injected into the dermis of the skin to elicit a stronger immune response. It has been shown that the antigen-presenting cells in the skin are more effective than the ones in muscle. ID rabies vaccination has been used successfully over decades and has saved millions of lives.

For further information please visit the [WHO Immunization, Vaccines and Biologicals webpage \(http://www.who.int/immunization/documents/policies/WHO\\_IVB\\_ISBN9789241513371/en/\)](http://www.who.int/immunization/documents/policies/WHO_IVB_ISBN9789241513371/en/)

## RABIES IMMUNOGLOBULIN

### Q.25 WHAT IS RABIES IMMUNOGLOBULIN (RIG) AND HOW IS IT USED?

Rabies immunoglobulin (RIG), is derived from the blood of humans (hRIG) or horses (eRIG). eRIG is highly purified and, when correctly administered, both hRIG and eRIG neutralize the virus at the wound site within a few hours. Although there are differences in the half-life of eRIG and hRIG, they are considered to have similar clinical effectiveness in eliminating the virus at the wound site.

*Skin testing before eRIG administration is not recommended and should be abandoned.*

RIG provides passive immunization and is indicated in individuals with category III exposures. RIG is administered only once in a lifetime, preferably at, or as soon as possible after, the initiation of post-exposure prophylaxis. RIG neutralizes the rabies virus at the inoculation site in the time before the immune system responds to the vaccine by production of rabies virus neutralizing antibodies.



RIG is not indicated in previously immunized individuals. Both active and passive immunization prevent the rabies virus from infiltrating the central nervous system, but become ineffective once the virus has crossed into the central nervous system. In most rabies-endemic settings availability of RIG is low, and its administration is cost-prohibitive.

*RIG is administered only once in a lifetime.*

#### THE MAXIMUM DOSE OF RIG IS CALCULATED AS FOLLOWS:

40 IU/kg body weight for equine RIG

20 IU/kg body weight for human RIG

#### THE MOST EFFECTIVE USE OF RIG IS IN THE WOUND

- *RIG administration is not indicated 7 days after the initial rabies vaccine administration*
- RIG is indicated in individuals with a category III exposure and individuals with category II exposure who are immunodeficient
- For small wounds, administer what is anatomically feasible while avoiding compartment syndrome
- For large and multiple wounds, dilute if necessary with physiological buffered saline to ensure greater wound coverage
- Only the amount necessary for infiltrating into and around the wound is administered
- The remainder of the calculated maximum dose of RIG does not need to be injected IM at a distance from the wound but can be fractionated in smaller, individual syringes for use in other patients. This requires aseptic retention and RIG should be used up or discarded by the end of the day
- Bat bites or scratches may not be easily visible or detectable. For exposures involving physical contact (i.e. a detectable bite or scratch) with a bat, RIG should be injected around the site of exposure to the degree that is anatomically feasible and possible.
- For mucosal exposures with no wound, further rinsing with diluted RIG can be considered.

#### Q.26 PRIORITIZATION OF RIG ALLOCATION

In many countries, RIG is expensive and in limited supply. Public health authorities' budget for RIG may be very limited or even absent. It is estimated that only around 1–10% of patients who need RIG receive RIG as part of PEP. Even in the absence of RIG, field data show that thorough wound washing with immediate administration of vaccine and completion of the PEP course saves up to 99% of patients exposed to the rabies virus.

*Vaccines should never be withheld, regardless of availability of RIG.*

If a limited amount of RIG is available, its 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, hands, genitals;

- patients with severe immunodeficiency;
- patients bitten by an animal with confirmed or probable rabies; and when

a bite, scratch, or mucous membrane exposure to a bat can be ascertained.

#### Q.27 IS IT NECESSARY TO PERFORM A SKIN SENSITIVITY TEST WHILE USING ERIG?

Modern eRIG is highly purified, and is considered to be clinically as effective as hRIG in eliminating the virus at the wound site within hours. In addition, eRIG is more widely available and less expensive than hRIG. For these reasons *skin tests should not be performed* before administration of eRIG. Skin tests poorly predict severe adverse events and should not be the basis for withholding eRIG if it is needed. All RIG should be administered under conditions that would allow management of an anaphylactic reaction.

#### Q.28 WHAT PRECAUTIONS SHOULD BE TAKEN WHILE ADMINISTERING RIG?

Although rare, treatment with any biological product risks an adverse immune reaction. Emergency medicines and facilities for managing adverse reactions should therefore be readily available, and physicians must be prepared to treat such reactions. Patients should be advised of potential adverse reactions; however, it is pertinent that they continue treatment regardless of any adverse effects, due to the risk of fatality from contracting rabies.

*RIG administration is not indicated after day 7 of PEP initiation*

- RIG vials taken out of a refrigerator should be kept outside for a few minutes before administration to the patient (to warm to room or body temperature).
- RIG should not be administered in the same syringe as the vaccine, or at the same site as the vaccine.
- Analgesics can be used to enable infiltration of RIG into the wound site.
- In small children or individuals with large or multiple bites, RIG should be diluted with physiological buffered sterile saline to increase the volume for infiltration in and around all wounds, taking care not to exceed the maximum calculated dose
- RIG should preferably be administered before administering the anti-rabies vaccination.
- While infiltrating RIG into bite wounds, care must be taken to avoid injecting into blood vessels and nerves. Anatomical feasibility must always be kept in mind while injecting RIG.
- While injecting into finger tips, pinna, nose or similar sites, care must be taken to avoid compartment syndrome, e.g. if large volumes of RIG are injected into a small body area with limited tissue.
- Administering RIG into subcutaneous fat reduces or delays effectiveness. Injection of RIG into the central gluteal area should be avoided due to the risk of damage to the sciatic nerve.
- Observe patients after RIG administration; severe adverse reactions, if any, usually occur within minutes.

Pregnancy is not a contraindication for RIG and anti-rabies vaccination.

### MANAGEMENT OF CLINICALLY AFFECTED PATIENTS

#### Q.29 WHAT PALLIATIVE CARE IS AVAILABLE FOR RABIES PATIENTS?

Although almost all clinical rabies patients will die, healthcare providers still have an essential role in providing prompt, effective, holistic, compassionate management in a culturally-sensitive way. This should be discussed with

the family as early as possible once the diagnosis has been made. This can be performed even with extremely limited equipment and medicines.

Given the inevitability of death in most rabies cases, treatment should focus on comfort, with heavy sedation barbiturates, morphine and *avoidance of intubation or life-support measures*, especially once the diagnosis is certain.

Patients with confirmed rabies should receive adequate hydration, sedation and care in an appropriate medical facility, preferably in a calm, draft-free and quiet room, with suitable emotional and physical support.

*The privacy, dignity and cultural needs of patients should be respected. Preserving the capacity of the family to communicate with their loved ones in their dying moments should be a priority.*

Further information on palliative care for rabies patients can be found in Chapter 6 of the WHO Expert Consultation on Rabies (3<sup>rd</sup> report): [http://www.who.int/rabies/resources/who\\_trs\\_1012/en/](http://www.who.int/rabies/resources/who_trs_1012/en/).

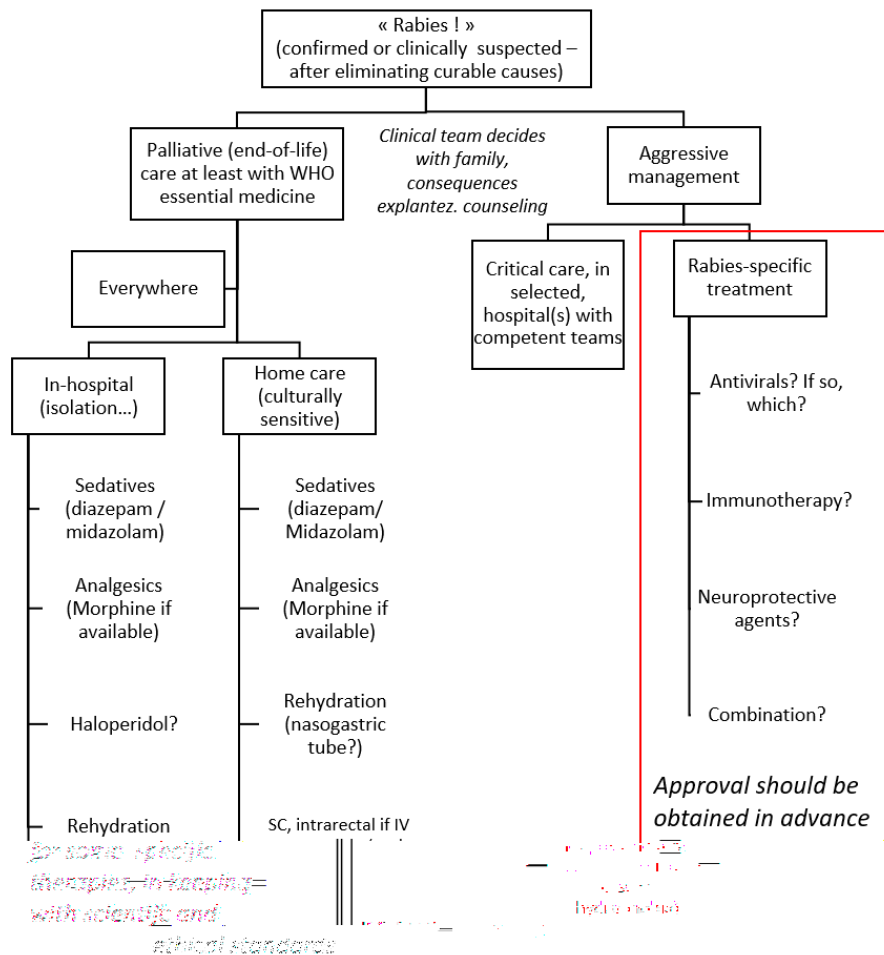


Figure 4. Proposed algorithm to guide management of cases of confirmed or suspected human rabies (WHO Expert Consultation on Rabies Third Report, 2018)

## **Sources**

1. WHO. WHO Expert Consultation on Rabies, third report: WHO Technical Series Report No.1012, Geneva, 2018, ISBN 978-92-4-121021-8.
2. WHO. Rabies Vaccines: WHO Position Paper - April 2018. Weekly Epidemiological Record, No 16, 2018, 93, 201–220.
3. WHO. The Global Strategic Plan to End Human Deaths from Dog-Mediated Rabies By 2030.  
[http://www.who.int/rabies/United\\_against\\_Rabies/en/](http://www.who.int/rabies/United_against_Rabies/en/)