

Post-exposure prophylaxis against rabies

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A. Procedure to be taken in response to a possible exposure to rabies

1. EVALUATION OF THE RISK OF EXPOSURE TO RABIES BY THE ATTENDING PHYSICIAN

Three questions must be answered in each evaluation:

- What is the probability that the animal had rabies?
- What type of risk category has the patient entered?
- What is the history of the patient?

1.1. Evaluation of the risk of rabies in the animal

1.1.1 Rabies in animals in endemic countries

Rabies is still endemic in more than 150 countries and is especially prevalent in dogs and in wild animal species.

- You can use this link to evaluate the risk for each country:
https://apps.who.int/neglected_diseases/ntddata/rabies/rabies.html
- Australia and the countries of Western Europe are considered non-endemic.
- In Bosnia and Herzegovina rabies has returned.
- In Mexico there is no more rabies in dogs (last update Sept 2020).

The following groups of animals bear an increased risk of rabies. We classify them as follows:

- **Wild land mammals (such as fox, wolf, monkey, raccoon ...)** in endemic areas or with suspicious symptoms in non-endemic areas.
The risk of rabies transmission in monkeys is relatively low, but not non-existent.
- **Dog, cat and ferret** in endemic areas, with suspicious symptoms in non-endemic areas, or if imported from endemic areas.
- **Bat** from endemic and non-endemic countries.
- In principle, there is virtually no risk of rabies in rodents.

1.1.2 The occurrence of rabies in animals in Belgium

In Belgium rabies only occurs in bats and - exceptionally - in (illegally) imported mammals.

Since 1922, only imported cases have been detected in humans.

Since July 2001, Belgium has been officially free from classical rabies in terrestrial animals, as stated by the World Organisation for Animal Health (OIE).

The virus, however, does circulate amongst bats in Belgium. In 2016 a rabies infected bat was found in Belgium near Bertrix.

1.1.3 Rabies in other countries

In Europe, between 2006 and 2011, there were twelve cases of rabies in seven countries of the European Union, including six imported cases. The infection in these cases was caused by rabid dogs, cats and bats.

1.1.4 The animal (live or cadaver) is available for follow-up

In the event of a bite with a suspect animal (imported animal or bat) within Belgium, always inform the medical inspector (see contact information below), who will contact the FAVV to evaluate the risk from the animal.

Depending on the decision of the FAVV veterinary surgeons, the animal will be euthanised or placed under observation for ten days.

If the animal is dead, a post-mortem diagnosis can be performed at the National Laboratory for Rabies.

The rabies PEP treatment is started according to the appropriate schedule and is only stopped if and when the possibility of rabies in the animal is excluded.

1.2. Evaluation of the contact of the animal with the skin

WHO EXPOSURE RISK CATEGORIES	
Category I	<ul style="list-style-type: none">• Tactile contact (stroking) or feeding the animal• Licking of the intact skin <p><i>In other words: no exposure</i></p>
Category II	<ul style="list-style-type: none">• Gnawing the uncovered and originally intact skin• Superficial lesions from scratches or grazes, without bleeding.• Licking of non-intact skin
Category III	<ul style="list-style-type: none">• Single or multiple bites or scratches that penetrate the dermis• Contact with the mucous membranes via the saliva after licking• Licking a grazed or broken skin• (Possible) scratches and bites of bats: often no visible lesion or the feeling of a bite

1.3. Evaluation of the patient's history

1.3.1 Already received a complete pre-exposure prophylaxis (PrEP) in the past.

Patients who have already received preventive rabies vaccination (pre-exposure prophylaxis) for their risk/journey should also receive booster vaccinations, for which see the 'Rabies PEP schema 1' (rabies PEP schedule 1) table. The PrEP schedule currently consists of two vaccination moments: Day 0 and Day 7, each involving either one intramuscular injection of the full dose, or two simultaneous intradermal doses of 0.1 ml at two different sites. The PrEP schedule is complete after the second vaccination, even if it takes place much later than Day 7. No repeat vaccinations should be provided for the trip: this two-visit schedule is life-long 'boostable'.

PrEP vaccinations should be encouraged for travellers who travel frequently or for a longer period of time to remote rural development areas, as well as for classic risk groups such as veterinarians, hunters, foresters and cavers. Travelers who undertake bicycle tours or trials, who visit monkey temples or small children who live in endemic areas, should strongly consider vaccination.

In individuals who have already received rabies PrEP, the immunological response after additional vaccinations (for rabies PEP) will be better (in terms of higher antibodies, faster increase of antibodies and a better affinity of the anti-rabies antibodies) than in patients who have never been vaccinated and who are to be started *de novo* with a rabies PEP schedule 2 or 3 (see table).

1.3.2 Immunocompromised patients

Immunocompromised patients should always receive a rabies PEP schedule 3 with immunoglobulins - regardless of whether they have already been PrEP vaccinated - following a Category II or III risk. PrEP for immunocompromised patients consists of a three-visit schedule (Day 0, 7, 28).

The categories of immunosuppression are described in Section 2 of the recommendations of the Superior Health Council, HGR No. 6561 - Vaccinaties van immuungecompromitteerde en chronische zieke kinderen en volwassenen (Vaccinations of immunocompromised and chronically ill children and adults).

2. MEDICAL CARE

2.1. Treating the lesion

1. Thoroughly clean the lesion (however small or superficial it might be) with plenty of soap and water (since the virus is very sensitive to detergents) for 15 minutes. Rinse abundantly.
2. Debridement of the lesion and careful disinfection (iodopovidone products).
3. If possible, delay stitching the wound.
4. Repeat tetanus vaccine and start antibiotics (of the amoxicillin-clavulanic acid type) if necessary.
5. For monkey bites (risk of herpes virus B in macaques), start antiviral therapy (Valacyclovir 5x 800 mg per day for seven to fourteen days).
6. No indication for special hygienic measures when caring for the patient during the incubation period.

2.2. Choice of the therapeutic schedule

You can discuss the indication for post-exposure prophylaxis against rabies and the choice of the therapeutic scheme by telephone with a doctor from the Institute of Tropical Medicine (see contact details below).

If the patient requires immunoglobulins (MARIG) according to the following schedule for their treatment, the patient must be referred to the ITG (Institute of Tropical Medicine) in Antwerp or, if outside working hours, to the emergency department of the Antwerp University Hospital (Universitair Ziekenhuis Antwerpen).

2.2.1 Choice of rabies PEP schedule if there was complete pre-exposure vaccination in the past

Because preventive vaccination (pre-exposure prophylaxis) does not provide complete protection, PEP booster vaccinations (rabies PEP schedule 1) are necessary for vaccinated individuals following a type II or III contact.

SELECTION OF RABIES PEP SCHEDULE IF COMPLETE PRE-EXPOSURE VACCINATION WAS GIVEN IN THE PAST

A patient who received a complete and reliable preventive vaccination in the past (at least a two-visit schedule) and who must start rabies PEP following a risk contact. This person is considered to be a lifelong 'boostable'.

SCHEDULE 1

Two vaccine doses

Day 0, 3
(no MARIG) (no RFFIT)

Four vaccine doses: 0.1 mL intradermally

DAY 0
(no MARIG) (no RFFIT)

2.2.2 Choice of rabies PEP schedule for a patient lacking pre-exposure vaccination

Following mucosal contact with saliva of a potentially rabid animal without injury (category III), MARIG is no longer indicated. In these cases only active immunisation is started (in addition to proper wound care).

CHOICE OF RABIES PEP SCHEDULE FOR A PATIENT LACKING PRE-EXPOSURE VACCINATION

ANIMAL	REGION	TYPE OF CONTACT	TREATMENT SCHEDULE
All animals <i>For bats, see below in this table.</i>	All countries	Category I	No rabies PEP
Rodents, rabbits, hares, animals other than mammals	All countries	Category II, III	No rabies PEP
Wild land mammals such as fox, wolf, monkey, raccoon ... <i>For bats, see below in this table.</i>	NON-ENDEMIC: Western Europe, Australia ...	Category II, III	No rabies PEP
	NON-ENDEMIC: Suspicious symptoms in land mammals	Category II, III	Consider rabies PEP
	ENDEMIC: (Country list) Eastern Europe, Africa, Asia, and North-, Central- and South America	Category II Category III for monkey	Rabies PEP schedule 2: Four vaccine doses: Day 0 (2x), 7, 21
		Category III (except for monkey)	Rabies PEP schedule 3: Five vaccine doses: Day 0, 3, 7, 14, 28 + MARIG Day 0 20 IU/kg #
Dog, cat, ferret	NON-ENDEMIC: Western Europe, Australia ...	Category II, III	No rabies PEP
	NON-ENDEMIC: Suspicious symptoms	Category II, III	Consider rabies PEP
	NON-ENDEMIC BUT THE ANIMAL WAS IMPORTED in the last 12 months and has unknown vaccination status	Category II	Rabies PEP schedule 2: 4 vaccine doses: Day 0 (2x), 7, 21
		Category III	Rabies PEP schedule 3: Five vaccine doses: Day 0, 3, 7, 14, 28 + MARIG D0 20 IU/kg #
	ENDEMIC: (Country list) Eastern Europe, Africa, Asia, and North-, Central- and South America.	Category II	Rabies PEP schedule 2: Four vaccine doses: Day 0 (2x), 7, 21
		Category III	Rabies PEP schedule 3: Five vaccine doses: Day 0, 3, 7, 14, 28 + MARIG D0 20 IU/kg #
Bat If the bat is available, contact the Rabies Laboratory	All countries	Scratch, bite or possible bite: always category III	Rabies PEP schedule 3: Five vaccine doses: D0, 3, 7, 14, 28 + MARIG 20 IU/kg #

MARIG Human anti-rabies immunoglobulins

RFFIT: neutralizing antibodies: rapid fluorescent focus inhibition test

Vaccination schedule (schedule 2, schedule 3 or other) without MARIG if PEP with vaccines already started more than 7 days previously

2.2.3 Rabies PEP schedules

HAS ALREADY HAD PRE-EXPOSURE VACCINATION (PREP)								
SCHEDULE 1								
	D0	D3	D7	D14	D21	D28	D+10	
2 vaccines / 2 visits Rabies PEP	1 x 	1 x 					No RFFIT	Contact category II and III (see table)
4 vaccines / 1 visit	 4x							
NO PRE-EXPOSURE VACCINATION (PREP) IN THE PATIENT HISTORY								
SCHEDULE 2								
	D0	D3	D7	D14	D21	D28	D+10	
4 vaccines / 3 visits Rabies PEP Without MARIG	2 x 		1 x 		1 x 		No RFFIT*	Contact category II Category III for monkeys (see table)
SCHEDULE 3								
	D0	D3	D7	D14	D21	D28	D+10	
5 vaccines / 5 visits Rabies PEP + MARIG + RFFIT	1 x  + MARIG 	1 x 	1 x 	1 x 		1 x 	RFFIT  Day 38	Contact category III Contact with bat Immune suppression (see table) Result RFFIT > 3.0 IU/ml Result RFFIT > 5.0 IU/ml (for bat or immune suppression)

LEGEND

-  1 injection 1.0 ml intramuscular
-  1 injection 0.1 ml intradermal
-  MARIG injection with immunoglobulins
-  RFFIT blood sample

* Exception: in fragile patients (children, elderly, chronic diseases, etc.) or when vaccination of uncertain quality was started abroad.

Timing of the treatment

The treatment is best administered between 24 and 48 hours after the risk exposure. If no medical treatment was given within this timeframe, the treatment should always be carried out regardless of the timing of the exposure to the risk.

The ideal administration of the PEP treatment is:

- Vaccination within 24 hours
- Human anti-rabies immunoglobulins (MARIG) within 48 hours and, at the latest, within 7 days of the start of post-exposure vaccination. No more immunoglobulins are given seven days after the start of the vaccination series. In contrast, MARIG is always administered if the vaccination sequence has yet to be started (e.g. more than 10 days after the risk bite).

New risk exposure within 3 months of previous PEP

If an adequate PEP schedule was given in the previous three months, wound measures are sufficient for a new risk exposure, and a new treatment with vaccinations and RFIT is not necessary.

Immunocompromised patients

A risk bite to an immunocompromised individual should always be treated with schedule 3: five vaccines over five visits and, on Day 0, injections with MARIG in and around the wound. Exception: if the animal was from a non-endemic area and had no suspicious symptoms. It is best to consult with a doctor from the ITG.

Bite wound with a high risk

Deep bites are high risk, as are bites on the head, face, neck or hand. It is best to consult with a doctor from the ITG.

Contraindications

Because rabies is a fatal disease, there is no contraindication for anti-rabies prophylaxis after high-risk exposure. The same applies to a post-exposure prophylaxis in the case of an infant, a pregnant woman or an immunocompromised individual.

Interchangeability of the vaccine

If it is not possible to complete the full schedule with the same brand of vaccine, another brand may be used. The WHO has documented the interchangeability of Verorab[®], Rabipur[®], HDCV Rabiës[®].

Interchangeability of the schedule

There are multiple rabies PEP schedules. If a patient presents with a different rabies PEP schedule after a trip, the rabies PEP schedule must be completed (with a four-part or five-stage vaccine schedule), preferably with no more than ten days of deviation between the follow-up injections.

Response to the PEP schedule

For a risk contact of category III, if there is immunosuppression, or if PEP was started abroad with doubt about the quality of the administered vaccinations, it is recommended to check for neutralising antibodies (RFFIT test) from the tenth day following the last anti-rabies vaccination. For this, a sample must be taken in a dry tube and sent to the National Reference Centre (NRC, WIV-ISP) via your laboratory. The analysis is paid for by the NRC (only for PEP-indications): use the attached application form.

For more practical details and for the application form, go to:
https://nrchm.wiv-isp.be/fr/centres_ref_lab/rabies_virus/default.aspx

The laboratory results should be interpreted as follows:

- After PEP, the serological response should be more than a RFFIT > 3.0 IU/ml.
- RFFIT values over 5.0 IU/ml should be sought in cases where there was contact with bats or if the patient was immunocompromised.

Stop PEP if the source is available for follow-up or analysis

PEP can be discontinued if the suspect animal appears rabies-free in laboratory analysis, or - in the case of a domesticated dog, cat or ferret - the animal remains healthy ten days after the risk exposure without signs of rabies.

RABIES VACCINES

Type

Two vaccines are registered in Belgium and are available from the pharmacy: Rabipur® en HDCV Rabiës® <http://www.bcfi.be/nl/chapters/13?frag=11387>.

Storage and transport

The vaccines have a storage life of more than 24 months and must be stored in a refrigerator (temperature from 2°C to 8°C).

Room temperature is acceptable during transport if this takes less than 3 hours. Transport is ideally at refrigerated temperature (2°C to 8°C).

Place of injection

The vaccine is given by intramuscular injection into the deltoid muscle or, in children younger than two years, in the anterolateral thigh muscle.

Availability

The rabies vaccines are available from the pharmacy and can be administered at a travel clinic, in and emergency room or at a general practitioner. The rabies vaccines are reimbursed in category B:

http://www.bcfi.be/nl/chapters/13?frag=17186&trade_family=22640

IMMUNOGLOBULINS (MARIG - HUMAN ANTI-RABIES IMMUNOGLOBULINS)

Type

At present, only BERIRAB® (Behring) is available, in ampoules of 2 and 5 ml and priced at about 110 € per ml. These immunoglobulins are not registered in Belgium. Ampoules of 2 ml, 300 IU/ampoule. Ampoules of 5 ml, 750 IU/ampoule.

Storage and transport

Room temperature is acceptable during transport if this takes less than 3 hours. If not, transport at refrigerated temperature (2°C to 8°C).

The MARIG have a storage life of more than 24 months and must be stored in a refrigerator (temperature from 2°C to 8°C).

Place of injection

The immunoglobulins are administered as soon as possible after the infection, whereby the largest possible amount is administered via a deep local injection in and around the bite with the aim of locally neutralising the virus. You can find a minimum and maximum volume to be injected for each anatomical location in the table below.

ANATOMICAL LOCATION	MARIG Minimum ml	MARIG Maximum ml
Finger/toe	2 ml	2 ml
Hand/foot	2 ml	4 ml
Knee/ankle/wrist/elbow	2 ml	6 ml
Forearm/lower leg	4 ml	10 ml
Upper arm/upper leg/torso	4 ml	10 ml*
Face/hairy scalp	2 ml	10 ml*
Mucous membrane	NONE	NONE

** Max. based on body weight (20IE/kg)*

Under the new WHO recommendations, MARIG administration at an anatomical site different from the site of the bite is no longer recommended.

In the past, the amount of MARIG to be administered was calculated on the basis of the patient's body weight. The maximum dosage of MARIG remains 20 IU per kilogram of body weight. The amount of MARIG depends on the anatomical location or locations of the injury and the size of the lesions, with a maximum dose still based on body weight.

The animal species also plays a role in the size of the wound. For example, a scratch or bite from a bat or a superficial cat scratch almost always leads to minor injuries (2 ml MARIG), as opposed to a full transdermal bite of a dog in a leg where the maximum dose (based on body weight) can be administered.

If the anatomical location really does not allow it or if the exposure region cannot be identified (in bats bites), MARIG is administered deep in the gluteal muscle.

Dosage: 20 IU/kg

The anti-rabies immunoglobulins can be diluted in physiological water to a volume sufficient to efficiently infiltrate all wounds.

	Weight 30 kg	Weight 50 kg	Weight 70 kg	Weight 90 kg
Berirab 300 IU 2ml	2 ampoules	1 ampoule		1 ampoule
Berirab 750 IU 5ml		1 ampoule	2 ampoules	2 ampoules
Total volume	4 ml	7 ml	10 ml	12 ml

Availability

Immunoglobulins against rabies are vital specialties that are not registered in Belgium and require a registered licence, which the UZA pharmacy will have from June 2017. These immunoglobulins have been fully reimbursable since July 2017 (Category A) with a signature from a physician attached to the Rabies Reference Centre (ITG). Immunoglobulins can only be administered at the ITG in Antwerp (during working hours). After working hours and during the weekend it is possible to get these immunoglobulins from the emergency department of the UZA, where ITG and UZA physicians jointly keep watch against infectious diseases.

B. Contact

1. THE RISK OF RABIES IN HUMANS

The Institute of Tropical Medicine (ITG) in Antwerp

Rabies expertise centre for Belgium authorised for post-exposure prophylaxis against rabies in patients

Telephone advice (on weekdays between 9 am and 5 pm) is available via the following numbers:

- +32-(0)3 247 6405
- +32-(0)3 247 6465
- +32-(0)3 247 6666

By e-mail medsec@itg.be

After working hours and during the weekend, contact the emergency department of the UZA (where ITG and UZA physicians jointly keep watch against infectious diseases):

- +32-(0)3 821 3000

National Reference Laboratory for Rabies (NRL-Rabies) of the WIV-ISP

- +32-(0)2-373 3111

MANDATORY NOTIFICATION OF THE HEALTH INSPECTORATE

Reporting of rabies is mandatory. In the case of a bite with a suspect animal (imported animal or bat) in Belgium, or if the patient develops symptoms (clinical, epidemiological and/or laboratory criteria), the attending physician must immediately inform the infectious disease physician. The latter is competent for the surveillance of communicable diseases in order to take ad hoc preventive measures, including contact with the FAVV and the National Laboratory for Rabies for an analysis of the risk in the animal.

Wallonia Region and the German-speaking Community

+32-(0)71 205 105

Brussels Capital Region

+32-(0)478 777 708

Flanders

During working hours

+32-(0)3 224 6204 (Antwerp)

+32-(0)11 742 240 (Limburg)

+32-(0)9 276 1380 (East Flanders)

+32-(0)16 666 350 (Flemish Brabant)

+32-(0)50 247 900 (West Flanders)

Outside working hours

+32-(0)2 512 9389

2. SUSPECT ANIMAL

Notify the following authorities:

Federal Agency for the Safety of the Food Chain (FAVV)

- +32-(0)474 802 803 (control veterinarian of the FAVV)

National Reference Laboratory for Rabies (NRL-Rabies) of the WIV-ISP

- +32-(0)2-373 3111

C. References

1. WHO RECOMMENDATIONS

WHO expert opinion on Rabies (April 2018)

http://www.who.int/rabies/resources/who_trs_1012/en/

WHO position paper on rabies vaccines (April 2018)

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

WHO Rabies Fact Sheet

<http://www.who.int/en/news-room/fact-sheets/detail/rabies>

Map showing occurrence of rabies in animals

<https://www.who-rabies-bulletin.org/site-page/epidemiology-rabies>

Map showing endemicity of dog-mediated rabies

https://apps.who.int/neglected_diseases/ntddata/rabies/rabies.html

2. CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC) RECOMMENDATIONS

MMWR 2010; **59(RR02);1-9**. Use of a Reduced (4 dose) Vaccine Schedule for Post-exposure Prophylaxis to Prevent Human Rabies: Recommendations of the Advisory Committee on Immunization Practices. <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5902a1.htm>

http://www.cdc.gov/rabies/resources/acip_recommendations.html

3. AGENCY FOR PUBLIC HEALTH SUPERVISION

Rabies guidelines

<https://www.zorg-en-gezondheid.be/rabi%C3%ABs-hondsdoelheid>

4. SUPERIOR HEALTH COUNCIL

HGR No. 6561 - Vaccinations of immunocompromised and chronically ill children and adults

<https://www.zorg-en-gezondheid.be/sites/default/files/atoms/files/immunogecompromitteerde%20en%20chronisch%20zieke%20kinderen%20en%20volwassenen.pdf>

5. NATIONAL INSTITUTE FOR PUBLIC HEALTH AND THE ENVIRONMENT

Rabies guidelines

<https://lci.rivm.nl/richtlijnen/rabies>

6. UK HSA

UK rabies risk by country

<https://www.gov.uk/government/publications/rabies-risks-by-country/rabies-risks-in-terrestrial-animals-by-country>

D. Abbreviations

IU	International units
IM	Intramuscular
ITG	Belgian Institute of Tropical Medicine
IU/ml	International units per millilitre
MARIG	Human Anti-Rabies Immunoglobulin (RIG)
OIE	World Organization for Animal Health
PEP	Post-exposure prophylaxis
PrEP	Pre-exposure prophylaxis
RFFIT	Rapid Fluorescent Focus Inhibition test
UKHSA	United Kingdom Health and Security Agency
UZA	Antwerp University Hospital
V	Vaccine dose
WHO	World Health Organization

E. Appendices

APPENDIX E1 - RISK SCHEDULE

ANIMALS	CATEGORY I	CATEGORY II	CATEGORY III	IMMUNE SUPPRESSION CATEGORIES II and III	Rabies- PrEP in good order
WILD LAND MAMMALS SUCH AS FOX, WOLF, RACOON ...					
Endemic	None	SCHEDULE 2	SCHEDULE 3	SCHEDULE 3	SCHEDULE 1
Non-endemic: Suspected	None	SCHEDULE 2	SCHEDULE 3	SCHEDULE 3	SCHEDULE 1
Non-endemic: Not suspected	None	None	None	None	None
MONKEY (WILD)					
Endemic	None	SCHEDULE 2	SCHEDULE 2	SCHEDULE 3	SCHEDULE 1
DOG, CAT, FERRET					
Endemic	None	SCHEDULE 2	SCHEDULE 3	SCHEDULE 3	SCHEDULE 1
Non-endemic: (Imported fewer than 12 months previously)	None	SCHEDULE 2	SCHEDULE 3	SCHEDULE 3	SCHEDULE 1
Non-endemic: Suspected	None	SCHEDULE 2	SCHEDULE 3	SCHEDULE 3	SCHEDULE 1
Non-endemic: Not suspected	None	None	None	None	None
BAT					
Endemic and non-endemic:	None* or Schedule 3	SCHEDULE 3	SCHEDULE 3	SCHEDULE 3	SCHEDULE 1

- No rabies PEP
- Schedule 1: vaccination Day 0 and Day 3 or intradermal vaccination (4x 0.1 ml) on Day 0
- Schedule 2: vaccination Day 0 (2x), Day 7, Day 21
- Schedule 3: MARIG Day 0 + vaccination Day 0, 3, 7, 14 and 28
- Rabies PrEP in good order: rabies pre-exposition prophylaxis in good order before the bite (Day 0 and 7)

* To be discussed with the ITG expert

Non-endemic - suspect animal: a PEP schedule may be considered if suspicious symptoms in the animal are identified by an expert. Or the animal remains under observation to monitor the development of suspicious symptoms.

