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# Time of administration of rabies immunoglobulins and adequacy of antibody response upon post-exposure prophylaxis: a descriptive retrospective study in Belgium

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**ABSTRACT**

**Background**: Data on rabies post-exposure prophylaxis (PEP) and the use of human rabies immunoglobulins (HRIG) in Belgium are scarce. The main objective of this study was to evaluate the timely administration of HRIG after rabies exposure. The secondary objective was to evaluate the adequate antibody response following PEP.

**Methods**: We reviewed all medical records from July 2017 to June 2018 of patients seeking care at, or referred to, the Institute of Tropical Medicine and the University Hospital, Antwerp for the administration of human rabies immunoglobulins following potential rabies exposure abroad or in Belgium.

A timely response was defined as starting HRIG with a delay of ≤48 h and rabies vaccination in the first 7 days after exposure.

Adequate antibody response was defined as a titer of >5.0 IU/mL in case of bat-related exposure and >3.0 IU/mL in case of exposure to other animals. Titers were measured 10 days after the last PEP vaccine dose, using the rapid fluorescent focus inhibition test (RFFIT).

**Results**: Of the 92 cases treated with HRIG, 75 were evaluated.

The majority of injuries were acquired in Asia (n = 26,34%) and in Western Europe (n = 18, 24%), of which 17 in Belgium. The five most frequently recorded countries overseas were Indonesia (n = 13), Thailand (n = 7), Morocco (n = 4), Peru (n = 3) and Costa Rica (n = 3). Administration of immunoglobulins was related to injuries by dogs (36%), monkeys (25%) or bats (22%).

A timely response was observed in 16 (21,33%) and in 55 (73,33%) of subjects receiving HRIG (≤48 h) or rabies vaccine (<7days) respectively. The mean time between exposure and the first administered dose of rabies vaccine and HRIG was 7.7 and 8.7 days, respectively. The mean delay for HRIG administration was 9.6 days and 6 days for abroad and inland risks, respectively.

In 15 of 16 (94%) bat-related cases the antibody titer after full PEP was >5.0 IU/ml. In 38 of 47 (81%) cases related to other animals the RFFIT titer was >3.0 IU/ml. All low-responders received additional rabies injections.

**Conclusion**: This study showed a substantial time delay between the animal-related risk and the administration of HRIG, in particular when the injury occurred abroad. More targeted communication about the risks of rabies and preventable measures may reduce this delay.

Furthermore, the antibody response was inadequate in some cases following full PEP administration according to the Belgian recommendation.

**KEYWORDS**
Rabies; pre-exposure prophylaxis; post-exposure prophylaxis

## Introduction

Rabies is a preventable neglected tropical disease with a very high case-fatality rate [1]. The annual death toll is approximately 61.000 cases, 40% of them occurring in children, with higher prevalence in Asia and Africa [2,3].

In Belgium, terrestrial mammals have been declared free of rabies since 2001, but contact with bats holds a risk of transmission. In Belgium, two bats were found in 2016 and 2017 to be infected with European bat lyssavirus-1, a virus which can also cause rabies in humans [4]. In France, rabies in bats is under surveillance since 1989, with 77 positive cases reported between 1989 and 2016 [5,6].

Although 60 cases of human rabies in international travelers were reported over a period of 22 years [7], travel to many endemic countries is associated with

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a very low risk of rabies (< 1/1.000.000) but with a high risk of an animal-related injury (>1/1000 and < 1/100) [8–10].

The World Health Organization (WHO) strictly recommends to immediately initiate rabies post-exposure prophylaxis (PEP) with or without human rabies immunoglobulins (HRIG), after an individual risk assessment [11–13]. HRIG administration serves to neutralize the virus locally, prevent its spread and span the period of the 7 to 10 days necessary to develop adequate antibodies response after rabies vaccination. Notably, HRIG are expensive and often difficult to obtain in endemic low-resourced countries, frequently resulting in stressful situations following an animal-related injury abroad.

The detailed Belgian guidelines on post-exposure prophylaxis (2017) are published on the ITM website [14].

- Since July 2017, the outpatient clinic of the Institute of Tropical Medicine, Antwerp (ITM) and the University Hospital of Antwerp (UZA) are the only Belgian centers authorized to administer HRIG in patients exposed to the disease [15]. Both ITM and UZA are located in Flanders.

- Human rabies immunoglobulins (HRIG) are only needed in non-rabies-vaccinated individuals and mainly indicated for category III lesions encountered by an at-risk animal (e.g. dog, monkey, cat, fox) in an endemic region (e.g. Asia or Africa). Category III lesions are defined as single or multiple transdermal bites or scratches of animals, licks on broken skin, or contamination of mucous membrane with saliva from licks. Furthermore, a category III exposure also corresponds to any direct contact with bats (with or without a skin lesion) [11].
- Passive immunization with (HRIG) (20 IU/kg of Berirab® vials of 2.0 mL or 5.0 mL) is performed by injection in and around the wound and the remaining volume in the adjacent limb. In addition, HRIG should be administered as soon as possible and preferably within 2 days after a potential rabies risk, and not anymore 7 days after the start of rabies vaccination.
- Additional active immunization with five injections of 1.0 mL rabies vaccine are administered at day 0, 3, 7, 14 and 28 ($5^1$1IM PEP schedule: 1 intramuscular injection (IM) during five different visits)(schedule 3: see figure).
- Antibody titers by rapid fluorescent focus inhibition test (RFFIT) are in Belgium always measured in a subject receiving HRIG, preferably 10 days after the last vaccine dose (usually at day 38 and the test is offered for free by the national reference laboratory) [14].

Table 1. Reporting and interpretation of RVNA serology results following post-exposure prophylaxis.

| RVNA level (RFFIT) | Protection level |
|---|---|
| < 0.5 IU/mL | No immune response against rabies |
| 0.5–2.99 IU/mL | Weak immune response against rabies |
| 3-10 IU/mL | Good immune response against rabies |
| > 5 IU/mL | Good immune response against bat-related risks |
| > 10 IU/mL | Very good immune response against rabies |

Interpretation of rabies serology values by the Scientific Institute of Public Health, Brussels – Sciensano.
RVNA: rabies virus neutralizing antibody – RFFIT: rapid fluorescent focus inhibition test.

- RFFIT titers are tested in Belgium at the national reference laboratory and need to be >5.0 IU/mL and >3.0 IU/mL, in bat-related injuries and all other animal-related injuries, respectively, [4,14] (Table 1).

An adequate rabies antibody response after PrEP or PEP, as measured by RFFIT, is internationally defined and accepted as a titer above 0.5 IU/mL This titer corresponds approximately to a cut-off of 1/15 serum dilution giving 50% in-vitro neutralization of 100 infectious particles, which is close to the limit of detection of the assay. No consensus exists between experts on how high geometric mean titer levels must be 7 or 14 days following booster vaccination to provide full protection against rabies after a risk. Unique in Belgium, the National Institute of Health (Sciensano) recommends stronger immune responses following PEP: for all risks, a RFFIT of >3.0 IU/mL is recommended wich corresponds approximately to a cut-off of 1/90 serum dilution giving 50% in-vitro neutralization of 100 infectious particles. For potential risks related with other lyssavirus species like European bat lyssaviruses an even higher minimal RFFIT titer of >5.0 IU/mL following PEP seems to be more prudent since cross-neutralization with the rabies vaccine strain is only partial [16,17]. All low-responders should receive additional rabies injections.

- The HRIG (Berirab®, CSL Behring) and the rabies vaccines (purified chicken embryo cell vaccine, PCECV, Rabipur®, GlaxoSmithKline Biologicals and human diploid cell vaccine, HDCV, HDCV Mérieux®, Sanofi Pasteur), are registered in Belgium and are stored between +2 and +8° C as recommended by the manufacturers.

The main objective of this study was to evaluate the timely administration of HRIG after rabies exposure. A secondary objective was to evaluate the antibody response 10 days following the completion of PEP.

## Methods

For this study, we reviewed all medical records from July 2017 to June 2018 of patients seeking care at, or referred to, the ITM or UZA for the administration of human rabies immunoglobulins following rabies

exposure abroad or inland. The Belgian guidelines on rabies post-exposure prophylaxis published in 2017 were strictly followed.

We reviewed the information in the records, including pre-exposure prophylaxis status, type of contact with an animal, type of animal, country of exposure, used rabies PEP schedule, and timing of administration after risk, as well as the final result of the RFFIT following PEP.

A timely response was defined as starting HRIG with a delay of ≤48 h and rabies vaccination in the first 7 days after exposure.

Adequate antibody response was defined as a titer of >5.0 IU/mL in case of bat-related exposure and >3.0 IU/mL in case of exposure to other animals. Titers were measured 10 days after the last PEP vaccine dose, using the rapid fluorescent focus inhibition test (RFFIT).

All patient data were pseudonymized and entered in a Microsoft Access File. Minimal criteria for inclusion in this retrospective analysis were defined as HRIG administration in Belgium, completeness of data on patient characteristics, risk information (bite category, animal, country), and timing of risk and vaccination schedule. Statistical analysis was performed with the STATA software.

## Results

Of the 92 medical records available for analysis, 75 were included for analysis; 17 records were excluded because HRIG had been administered abroad (n = 9), or data were incomplete (n = 8).

All included participants received HRIG injected in and around the wound and the remaining volume in the adjacent limb. A median of 10 mL (range: 2–15 mL) of HRIG per case was used.

In addition, 5 injections of 1.0 mL PCECV, were given at day 0, 3, 7, 14 and 28 ($5^{1}$IM PEP). The PCECV shots on day 3, 7, 14 and 28 were mainly performed outside the ITM or UZA, by the family doctor.

Forty-four of the cases (58%) were female. Mean age was 33 years (interquartile range 24–51; range: 4–85). Patients were transferred to our centers from different regions: 65% of patients were living in Flanders, 15% in Brussels and 25% in Wallonia.

During the 2017 summer, including the 2-month school holidays of July and August, 40 patients (55%) received HRIG (six cases per month in average; see Table 2).

The most frequently reported continents of exposure to risk were Asia n = 26 (34%), Western-Europe n = 18 (24%), Belgium n = 17 (23%), and Africa n = 12 (16%). The five most frequent recorded countries overseas were Indonesia (n = 13), Thailand (n = 7), Morocco (n = 4), Peru (n = 3) and Costa Rica (n = 3).

Injuries were related to dogs, monkeys, and bats in 36%, 25% and 22% of cases respectively. Monkey-bites were encountered as the most frequent risk in different Asian countries (Indonesia and Thailand), as were bat-bites in Belgium. Two cases were related to a rabies-positive dog from Morocco.

Ninety-nine percent of exposures were classified to be category III, of which 17 cases (23%) were related to bat-encounters.

Of the 75 evaluated subjects, 64 (85%) subjects started their PEP schedule with HRIG at ITM and 11 subjects (15%) at the UZA.

Ninety-six percent of 75 completed a $5^{1}$IM PEP schedule over 28 days together with HRIG. Three patients started different PEP schedules overseas, of which one followed the $3^{2+1+1}$IM PEP schedule (3 visits (2-1-1) over 21 days). All included subjects received HRIG within 7 days after the start of the first rabies vaccination. All of them completed their $5^{1}$IM PEP schedule.

In this cohort, a timely response was observed in 16 (21%) and in 55 (73%) of subjects receiving HRIG (≤48 h) or rabies vaccine (<7days) respectively. Furthermore, the mean time between exposure and the administered HRIG was 8.7 days: 9.6 days (IQR 2,5–9) and 6 days (IQR 1–4) for abroad and inland risks, respectively. The mean time delay between exposure and the first administered dose of rabies vaccine was 7.7 days: 8.3 days (IQR 0–8,5) and 6 days (IQR 1–4) for abroad and inland risks, respectively.

A total of 63 (84%) participants were subjected to RFFIT testing approximately 10 days after the last vaccination of PEP. One patient stopped the vaccine series prior to finalization of PEP after the brain biopsy of the offending dog excluded rabies. The median timing of RFFIT testing after the last vaccine dose was 12 days.

A total of 15 of 16 subjects (94%) exposed to bats displayed after a full five-dose PEP regimen a RFFIT >5.0 IU/mL; 38 of 47 subjects (81%) with other animal-related injuries displayed a RFFIT >3.0 IU/mL: this difference was not significant. One single patient of the 63 subjects had no response (RFFIT <0.5 IU/mL) after a full $5^{1}$IM PEP schedule, probably related to old age (80 years old), although the timing of the vaccinations and the serology test were in accordance to the standard protocol. The 10 cases with low or no antibody response received additional vaccine shots.

## Discussion

This study highlights a substantial mean delay of 8.7 days between the animal-related risk and the administration of HRIG, in particular when the risk occurred abroad (9.6 days versus 6 days for inland exposure). Also, the antibody response was inadequate in some cases following full PEP administration following the Belgian recommendation.

Table 2. Rabies PEP Schedules in BE.

| Schedules | D0 | D3 | D7 | D14 | D21 | D28 | D + 10 | Indications |
|---|---|---|---|---|---|---|---|---|
| **Rabies PEP after PrEP** | | | | | | | | |
| **Schedule 1:**<br>2 intramuscular injections/2 visits<br>4 intradermal injections/1 visit<br>1 injection = 0.1 mL | 1 x<br>1 x | 1 x | | | | | No RFFIT | Contact category II en III |
| Rabies PEP without previous PrEP | | | | | | | | |
| **Schedule 2:**<br>4 intramuscular injections/3 visits | 2 x | | 1 x | | 1 x | | No RFFIT | Contact category II<br>Exception to do RFFIT on D31 if:<br>- vaccination schedule started overseas<br>- in 'vulnerable' patients |
| **Schedule 3:**<br>5 intramuscular injections/5 visits<br>+ Human rabies immunoglobulins (HRIG) | 1 x | 1 x | 1 x | 1 x | | 1 x | RFFIT<br>D38 | Contact category III<br>Result RFFIT > 3.0 IU/ml<br>Result RFFIT > 5.0 IU/ml (if bat-related or immunosuppression) |

PEP: post- exposure prophylaxis – PrEP: pre-exposure prophylaxis – RFFIT: rabies fluorescent focus inhibition test

PEP and HRIG should ideally be administered as soon as possible and preferably within 2 days after a potential rabies risk in order to obtain an adequate antibody response RFFIT >3.0 IU/mL within 7 days after exposure (following the Belgian recommendations) [4,12–14]. After a bite, the time between risk-to-adequate antibody response following vaccination is crucial to prevent human deaths, since rabies incubation may be as short as 5 to 7 days [1]. More targeted communication about the risks of rabies and preventable measures may reduce this delay.

There was an increase in use of HRIG in Belgium in the last year: from a steady 20 per year over the last years to over 80 indications during the study period. The increase in use of HRIG in Belgium can't be explained by a parallel increase in travel worldwide [18]. The targeted communication about the risks of rabies and preventable measures at the moment the service delivery was transferred to our institutions may have contributed to the increased number of PEP courses prescribed [10]. Indeed, detailed information related to the topic of rabies prevention (new PEP guidelines) was shared at this momentum with general practitioners, emergency physicians and pharmacists in 2017. Notably, press releases for the public in Belgium helped in increasing the overall awareness. In the past, there were also frequent stock problems of HRIG, limiting their use. In addition, HRIG are now permanently accessible (24/7) and administered according to the newly issued 2017 guidelines. There is also a new website (with guidelines) and experts on call, all measures that facilitate improved PEP management (https://www.itg.be/E/Article/rabies).

The referrals from Brussels and Wallonia were less frequent, than those from Flanders, and this was likely related to the non-central geographical situation of the national reference centers for rabies prevention and treatment. Targeted information sessions are probably needed in other Belgian regions to increase the awareness for animal-related risks during travel and for bat-related injuries in Belgium. A new Belgian website and application on travel medicine will be launched by the ITM in May 2019 (www.reisgeneeskunde.be), aiming to inform victims of animal-related injuries to take the appropriate steps.

Geographic distribution of animal-related injuries with mostly dog- and monkey-injuries in Asia and Africa were similar to observations from other studies [9,10].

The 5[1]IM PEP schedules were followed correctly in most cases and had good immunological responses for bat-injuries (94%) but a somewhat lower responses for other animal-related injuries (81%). Only one case, evaluated 10 days after the completion of the vaccine series, had no response at all (following the WHO recommendation) [11]. Starting rabies vaccination (active immunization) abroad and HRIG (passive immunization) at least 1 day later in Belgium could negatively have influenced the antibody response in some cases. Moreover, the quality processes of vaccine manipulation are not always guaranteed abroad. A Swiss retrospective study showed no responses in 6 of 90 patients (6.7%) after 4 doses of vaccine [12]. For all these reasons, the existing 5[1]IM PEP schedule and HRIG with the additional RFFIT test will remain unchanged for the moment, although other shorter PEP schedules were recently recommended by the WHO [11,13–15,20]. Although the Belgian recommendation to evaluate RFFIT levels 10 days following full PEP with the need of higher cut-off levels (>3.0 or >5.0 IU/mL) compared to international guidelines, is very unique, this practice underlines the importance of serology testing and additional vaccine injections (if needed) following risk exposure [4,13–15,20]. The WHO surprisingly recommends an identical cut-off titer of 0.5 IU/mL following PrEP (in prevention) and following PEP (in the treatment for a nearly 100% fatal disease). It should be emphasized that a titer of 0.5 IU/mL equals a very low level of neutralizing antibodies, close to the limit of detection of the assay and corresponding approximately to a 1/15 serum dilution giving 50% in-vitro neutralization of 100 infectious particles).

Bat-related contacts and/or injuries accounted for a sizeable proportion of our cohort. Although bat-related rabies is uncommon in Belgium and mostly related to the species *Eptesicus serotinus* with a transmission risk of European bat 1 lyssavirus, the full 5[1]IM PEP schedule together with HRIG is usually given with a very low threshold [4–6]. Active surveillance of rabies in bats, as done in neighboring countries, is worth considering in Belgium [5,6].

This study has several limitations. First, it was a retrospective analysis. Second, we couldn't include exposed cases with category III lesions, that were not referred and did not receive HRIG.

The Belgian rabies PEP guideline have been recently revised in 2019 [20,21](Table). Firstly, to limit the use of HRIG, they will be only administered in and around the wound and not anymore in the adjacent limb [11,13,14]. Following the new Dutch guidelines on rabies PEP, at least 2 mL of HRIG will be injected in wounds located in difficult extremities, e.g. finger or toe [14,22]. Secondly, injuries due to monkey bites, although very frequent, represent a very low risk of rabies transmission [23]. For this reason, the use of HRIG for monkey injuries is not recommended anymore in Belgium [14]. Finally, cases with a category III lesion, related to a mucosal contact, will be in general excluded from injections with HRIG and will receive a rabies vaccine schedule with four intramuscular

injections (figure: schedule 2: two injections on day 0, 1 on day 7 and one on day 21) [14].

WHO has also recently recommended rabies two-visit pre-exposure prophylaxis (PrEP) schedules instead of three-visit schedules, with the main aim to be cost-, dose- and time-sparing, while still assuring the safety and clinical effectiveness of these preventive interventions [11]. These two-visit PrEP schedules $2^2$ID appeared to be adequate, safe, and more convenient for travelers [24]. Furthermore, a single-visit PrEP schedule is an option for the last-minute traveler [25]. Both new rabies PrEP schedules have recently been implemented in Belgium and in general need to be more promoted in travelers visiting dog-related rabies endemic countries to simplify PEP procedures [26]. In addition, another important advantage of the PrEP is that individuals have higher and faster anamnestic responses, and higher affinity of specific antibodies against rabies, following a PEP booster, compared to non-primed individuals who have to receive a full $5^1$IM PEP schedule [27,28]. Newly introduced shorter PrEP regimens could increase travelers' adherence to this recommendation.

## Conclusion

This study showed a substantial delay in this Belgian cohort between animal-related risk and administration of HRIG, in particular when the injury occurred abroad. More targeted communication about the risks of rabies and preventable measures may reduce this delay Furthermore, the antibody response was inadequate in a few cases according to the Belgian recommendations.

## Author contributions

PS conceived the research project. PS, MC, SD, UM, CT, RH, EF, IB, CK, JVG, SVI, SVDB, JC, LL, EV, EB were the treating physicians of the patients at risk. CB analyzed the data. KB and MVE were responsible for the practical aspects of pharmaceutical and laboratory aspects. SVG was responsible for the laboratory analyses. PS, MC, SD, SVG, EB, YVH wrote the paper.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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