# Rabies post-exposure prophylaxis: A systematic review on abridged vaccination schedules and the effect of changing administration routes during a single course

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Vaccine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

# Rabies post-exposure prophylaxis: A systematic review on abridged vaccination schedules and the effect of changing administration routes during a single course

Joss Kessels [a], Arnaud Tarantola [b,c], Naseem Salahuddin [d], Lucille Blumberg [e], Lea Knopf [a,*]

[a] Department of the Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland
[b] Unité d'Epidémiologie, Institut Pasteur de Nouvelle-Calédonie, Nouméa, New Caledonia
[c] Unité d'Epidémiologie et de Santé Publique, Institut Pasteur du Cambodge, Phnom Penh, Cambodia
[d] The Indus Hospital Karachi, Karachi, Pakistan
[e] National Institute for Communicable Diseases, National Health Laboratory Service, Johannesburg, South Africa

ARTICLE INFO

*Article history:*
Available online xxxx

*Keywords:*
Rabies
Post-exposure prophylaxis
Updated WHO position
Systematic literature review
Vaccine

ABSTRACT

Rabies is a fatal zoonotic disease preventable through timely and adequate post-exposure prophylaxis (PEP) to potentially exposed persons i.e. wound washing and antisepsis, a series of intradermal (ID) or intramuscular (IM) rabies vaccinations, and rabies immunoglobulin in WHO category III exposures. The 2010 WHO position on rabies vaccines recommended PEP schedules requiring up to 5 clinic visits over the course of approximately one month. Abridged schedules with less doses have potential to save costs, increase patient compliance, and thereby improve equitable access to life-saving PEP for at-risk populations. We systematically reviewed new evidence since that considered for the 2010 position paper to evaluate (i) the immunogenicity and effectiveness of PEP schedules of reduced dose and duration; (ii) new evidence on effective PEP protocols for special populations; and (iii) the effect of changing routes of administration (ID or IM) during a single course of PEP. Our search identified a total of 14 relevant studies. The identified studies supported a reduction in dose or duration of rabies PEP schedules. The 1-week, 2-site ID PEP schedule was found to be most advantageous, as it was safe, immunogenic, supported by clinical outcome data and involved the least direct costs (i.e. cost of vaccine) compared to other schedules. To supplement this evidence, as yet unpublished additional data were reviewed to support the strength of the recommendations.

Evidence suggests that changes in the rabies vaccine product and/or the route of administration during PEP is possible. Few studies have evaluated PEP schedules in persons with suspect or confirmed rabies exposures. Gaps exist in understanding the safety and immunogenicity of novel PEP schedules in special populations such as infants and immunocompromised individuals. Available data indicate that administering rabies vaccines during pregnancy is safe and effective.


## 1. Introduction

Rabies is a fatal disease caused by the rabies virus (RABV) and other lyssaviruses and responsible for an estimated 59,000 human deaths every year [1]. Up to 99% of human cases worldwide are caused by dog bites [2]. Although there is no cure for clinical rabies, the disease is readily preventable through timely provision of adequate post-exposure prophylaxis (PEP).

PEP consists of thorough washing of the wound with water, soap and application of antiseptics [3]; a series of rabies vaccinations; and administration of rabies immunoglobulins (RIG) or more recently licenced monoclonal antibody products, if indicated [4]. The PEP protocol varies according to the category of exposure, the immunological status of the patient and whether they have been previously immunized against rabies [5]. As per 2010 recommendations, a previously immunized person refers to a person who has previously received rabies vaccine, either as a complete pre- exposure prophylaxis course or as PEP. For persons who are previously immunized against rabies, even decades earlier, RIG is not indicated, and only booster injections are recommended [4]. These will invoke an anamnestic response and boost antibody production.

* Corresponding author.
*E-mail address:* lea4knopf@gmail.com (L. Knopf).

https://doi.org/10.1016/j.vaccine.2019.01.041
0264-410X/

A rabies virus neutralizing antibody (RVNA) titre ≥0.5 IU/ml on day 14 post-immunization with rabies vaccine is internationally agreed as indicative of an adequate response to immunization. This threshold is a surrogate used to measure the vaccine-induced seroconversion in studies of rabies vaccine efficacy and effectiveness [5]. Rabies vaccines can be administered by the intradermal (ID) or intramuscular (IM) route, depending on the schedule. Intradermal rabies vaccination has been promoted by the World Health Organization (WHO) since 1992. Its use can reduce the cost and dose of vaccine by 60–80%, especially in high-throughput clinics [6,7].

Although rabies vaccines are considered safe and highly effective, WHO-recommended vaccine schedules of 2010 require up to five clinic visits over approximately one month (see Table 1) [4]. Due to the long duration of the schedule, persons potentially exposed to rabies often do not complete the full course of vaccination, with undetermined preventive effectiveness.

The high cost of rabies PEP and potential loss of income due to frequent travel to the clinic can pose a further barrier to treatment, particularly in low- and middle-income countries [8–10]. Additionally, healthcare workers may be reluctant to fractionate vials of rabies vaccine for patients if they are unsure the full volume will be used before it should be discarded (i.e. within 6–8 h), which can delay initiation of PEP. Shortages of rabies vaccines (and RIG) occur frequently, particularly in small clinics in rural areas of developing countries [11,12].

The 2010 WHO position paper [4] on rabies states that:

> "New PEP schedules, particularly those using ID administration, even if shown to be safe and efficacious, must have clear practical or economic advantages, or both, over existing schedules if they are to be endorsed."

The long duration of the schedule also means that changes in route of administration (IM to ID or vice versa) are likely to occur in practice, e.g. where patients receive first or continuing vaccine administration in a small clinic in a rural area (likely IM) after referral to or from a larger clinic (likely ID). It is therefore also of practical importance to assess the adequacy of the immune response conferred by changes in the PEP administration route, instead of beginning the schedule anew.

This systematic review on PEP aimed to inform the 2018 update of the WHO position on rabies vaccines and rabies immunoglobulins by evaluating: (i) the immunogenicity and effectiveness of PEP schedules of reduced dose and duration; (ii) new evidence on effective PEP protocols for special populations (immunocompromised, pregnant women) and (iii) the effect of changing routes of administration (ID or IM) during a single course of PEP on the immunogenicity of PEP. The literature search is intended as an update to the evidence review performed for the 2010 WHO rabies vaccine position paper [4].

## 2. Methods

The literature review was performed according to PRISMA guidelines for systematic reviews and meta-analyses [13]. We used the following terms to conduct a database search of the PubMed and Cochrane Database of Systematic Reviews (CDSR), respectively:

("Rabies Vaccines"[nm] AND "Humans"[MeSH terms]) AND ("post-exposure"[title/abstract] OR "postexposure"[title/abstract]) AND ("2008/01/01"[PDAT]: "3000/12/31"[PDAT])

and

#Rabies.

The search was conducted without language restrictions and included articles published between January 2007 and June 2017 to reflect evidence published after the literature review for the 2010 WHO position paper on rabies was completed and as a conservative approach to capture evidence where records of exact timeframes for previous literature reviews were lacking (Fig. 1) [4]. Reference lists were screened for additional relevant literature as supporting evidence for new PEP schedules, regardless of publication date. Relevant evidence from unpublished studies identified through screening of grey literature and as submitted for consideration by the Strategic Advisory Group of Experts on Immunization (SAGE) working group on rabies was also assessed for inclusion [14]. Titles and abstracts of all identified scientific publications, as well as references of eligible reviews, were screened for inclusion according to the criteria listed in Table 2.

## 3. Results

The literature search identified 13 relevant studies: seven studies relevant to PEP schedules of reduced doses/duration [15–21], four studies on PEP protocols for patients with specific medical conditions [22–25] and two studies relevant to changing the route of vaccine administration or product during the same course of PEP [26,27]. A then yet unpublished study from Cambodia with robust data on an abridged PEP schedule was also identified and included [28]. No direct evidence could be retrieved in support of an abridged version of the Essen IM regimen (3 or less doses). Several studies, including two cited in this publication [19,21], show immunogenicity data at intervals over the course of the established 4- or 5-dose IM PEP schedule as a comparator to investigational schedules.

**Table 1**
Summary of the 2010 WHO-recommended PEP schedules (prior to the 2018 update). These are recommended for persons with a category II or III exposure (plus RIG, if applicable).

| Schedule | Route | Sites | Days | Clinic visits | Duration (days) |
|---|---|---|---|---|---|
| *WHO approved PEP schedules for non-previously immunized persons*[a] | | | | | |
| 5-dose Essen (WHO 1992) | IM | (1-1-1-1-1) | 0, 3, 7, 14, 28 | 5 | 28 |
| Zagreb 2-1-1 (WHO 1992) | IM | (2-0-1-0-1) | 0, 7, 21 | 3 | 21 |
| Updated Thai Red Cross (TRC) (WHO 2005) | ID | (2-2-2-0-2) | 0, 3, 7, 28 | 4 | 28 |
| 4-dose Essen (ACIP 2009)[b] | IM | (1-1-1-1-0) | 0, 3, 7, 14 | 4 | 14 |
| *WHO approved expedited PEP schedules for previously immunized persons (booster)*[a] | | | | | |
| 2-visit PEP | ID/IM | (1-1-0-0-0) | 0, 3 | 2 | 3 |
| Single day PEP | ID | (4-0-0-0-0) | 0 | 1 | 1 |

[a] As per the 2010 WHO position, a previously immunized person referred to a person who can document previous complete course of pre-exposure vaccination or complete PEP.

[b] As per the 2010 WHO position, the 4-dose Essen schedule should be used only in healthy, immunocompetent patients who receive wound care, high quality rabies immunoglobulin, and WHO-prequalified rabies vaccines.

Please cite this article as: J. Kessels, A. Tarantola, N. Salahuddin et al., Rabies post-exposure prophylaxis: A systematic review on abridged vaccination schedules and the effect of changing administration routes during a single course, Vaccine, https://doi.org/10.1016/j.vaccine.2019.01.041

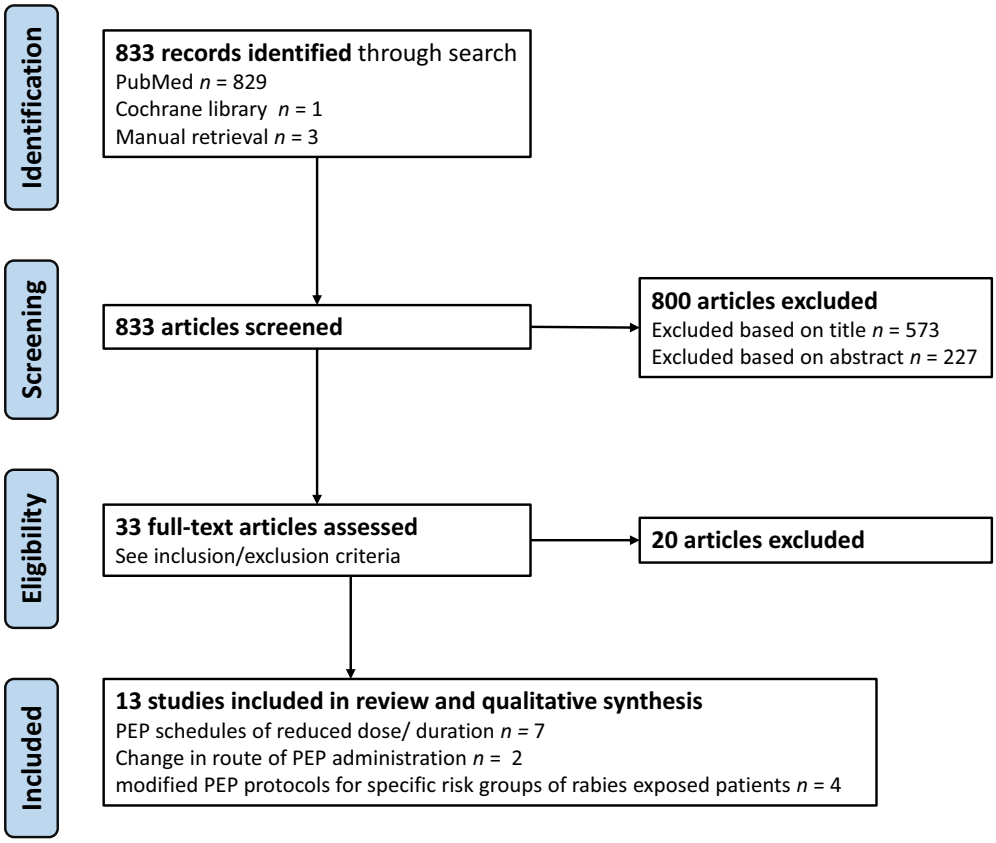


**Fig. 1.** PRISMA flow diagram showing the selection of studies on rabies post-exposure prophylaxis.

**Table 2**
Inclusion and exclusion criteria for evidence retrieved.

| Inclusion criteria | Exclusion criteria |
|---|---|
| Original studies | Guidelines |
| Review articles | Letters |
| Published in journals, books or websites | Editorials |
| Reported on abridged rabies vaccine schedules | Animal studies/basic research |
| Included estimates of efficacy, effectiveness, immunogenicity conferred by rabies immunization | Reports on schedules approved by WHO in 2010 |

### 3.1. PEP course duration and number of doses

A total of eight studies investigated the safety and immunogenicity of PEP schedules with reduced duration and/or number of doses compared to the PEP schedules recommended in the 2010 WHO position paper on rabies vaccines [15–21]. Their characteristics are summarized below and detailed study results are available in Table 3.

#### 3.1.1. 1-week, 4 site ID schedule (4-4-4-0-0)

Shantavasinkul et al. evaluated the safety and immunogenicity of a one-week ID schedule in 131 healthy volunteers [15]. The study included 3 arms, all which used purified Vero cell rabies vaccine (PVRV): (1) a 1-week, 4-site ID schedule in healthy, non-rabies exposed volunteers; (2) a 1-week, 4-site ID schedule plus equine rabies immunoglobulin (eRIG) in healthy, non-rabies exposed volunteers; and (3) a Thai Red Cross (TRC) schedule plus eRIG in patients with category III exposures from suspected rabid animals. All participants had RVNA concentrations ≥0.5 IU/ml on days 14 and 28. The proportion of subjects that had antibody concentrations ≥0.5 IU/ml on day 360 were similar across the three study arms. The 1-week, 4-site ID schedule showed increased immunogenicity compared to the 5-visit TRC-ID schedule on days 14 and 28.

Sudarshan et al. evaluated the safety and immunogenicity of this ID schedule in healthy, non-rabies exposed volunteers [16]. The study had 2 arms using (1) purified chick embryo cell rabies vaccine (PCECV); and (2) PVRV. All participants had RVNA concentrations ≥0.5 IU/ml at day 14, 28, and 180. The immune response was comparable to that induced by previously WHO-recommended PEP schedules. One-year post immunization, 78.9% of volunteers who received PCECV (arm 1) and 62.5% of those who received PVRV (arm 2) had RVNA concentrations ≥0.5 IU/ml. Volunteers with RVNA concentrations <0.5 IU/ml received booster doses i.e. 4-site ID vaccination on day 436 ± 16. All who received booster vaccination had RVNA concentrations ≥0.5 IU/ml by day 7 following booster vaccination. This quick anamnestic response to booster vaccination indicates the schedule induced strong immunological memory. No significant differences were present in the anamnestic RVNA response to PCECV compared to PVRV. The schedule was well-tolerated and adverse event rates were relatively low.

Narayana et al. evaluated the ID schedule in patients with category II and III exposures from suspected rabid animals [17]. The patients received either PCECV or PVRV. All subjects followed up had RVNA titres ≥0.5 IU/ml at day 14, 90 and 365; and all were alive and healthy on day 365. Patients with category III exposures across both study arms received eRIG. No significant difference was found between RVNA titres of patients who received eRIG compared to those who did not (i.e. patients with category II compared to category III exposures) or between patients who received PCECV and eRIG compared to PVRV and eRIG. The incidence of local and

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**Table 3**
Detailed overview on design, immunogenicity and effectiveness of identified studies on investigational PEP schedules for healthy persons.

| Author | Year | Schedule | Route | Sites | Days | Clinic Visits | Total Dosage (mL) | Duration (days) | Sample Size | Sample Specifics | Vaccine Used | Serology Results | Potency (IU/mL) | Limitations and Concerns | Exposure characteristics |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Huang et al. [18] | 2014 | 1-week/2 and 1 site IM | IM | (2-0-1-0-0) | 0, 7 | 2 | 1.5 (0.5 ml vial) 3.0 (1 ml vial) | 7 | 181 | 1. 79 in test group and 102 in control group (Essen)<br>2. 919 blood samples obtained out of 1086 sampling events scheduled due to poor compliance by control group at days 180 and 360<br>3. All had no prior antirabies vaccination | PVRV | 1. On day 14, all study subjects exhibited RVNA titres >0.5 IU/mL<br>2. RVNA titres were maintained in both groups through days 45 and 180 before gradually declining<br>3. The percentage of subjects positive for RVNA on day 7 was not statistically different between the test and control groups<br>4. On day 360, the percentage of subjects positive for RVNA in the variable and control groups were 93.9% and 100% respectively, which was statistically significant | 5.5 | 1. Schedule tested in healthy subjects<br>2. All study subjects were young adults between 18 and 26 years of age<br>3. The long-term persistence of immunity was slightly reduced following the 2-1 schedule compared with the five-injection schedule therefore clinical research is needed for comparison<br>4. Did not include vaccine combined with RIG | Healthy volunteers |
| Naranya et al. [17] | 2015 | 1-week/4-site ID | ID | (4-4-4-0-0) | 0, 3, 7 | 3 | 0.4-0.4-0.4 (total 1.6 ml) | 7 | 90 | 1. eRIG administered to all category III exposures<br>2. Randomized into 2 groups to receive either Rabipur or Verorab<br>3. Sociodemographic characteristics between groups were similar<br>4. All had no prior antirabies vaccination | Purified chick embryo cell (Rabipur) or PVRV | 1. Serum samples were collected on days 0, 14, 90, and 365<br>2. In the Rabipur group, the GMT of RVNA was 14.5, 11.78, and 5.96 IU/mL on days 14, 90, and 365 respectively<br>3. In the Verorab group, the GMT of RVNA was 14.43, 11.93, and 5.67 IU/mL on days 14, 90, and 365 respectively<br>4. 100% of the subjects had adequate >0.5 IU/mL RVNA concentrations from day 14 to day 365<br>5. Both the vaccines with or without eRIG had similar GMT RVNA concentrations | 6.9–7.5 | 1. Confirmation of rabies in the biting animals was not possible due to practical difficulties<br>2. Was not tested in children, pregnant, or lactating women | Volunteers with category II or III animal bites/exposures from suspected rabid animals (not lab confirmed) |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Shantavasinkul et al. [15] | 2010 | 1-week/4-site ID | ID | (4-4-4-0-0) | 0, 3, 7 | 3 | 0.4-0.4-0.4 (total 1.6 ml) | 7 | 131 | 1. All had no prior antirabies vaccination<br>2. The characteristics of subjects in each group were similar in terms of age and sex<br>3. Group A received test schedule Group B received test schedule and eRIG, and Group C were those with category III rabies exposures and received TRC-ID schedule and eRIG | PVRV | 1. RVNA levels were tested on days 0, 7, 14, 28, 90, 180, and 360<br>2. The overall pattern of antibody response was similar in each study group; highest on days 14 and 28 and slowly decreased up to day 360<br>3. All subjects who received the 4-site ID schedule had RVNA levels > 0.5 IU/mL on days 14 through 90<br>4. The GMT of RVNA in the 4-site ID schedule with and without eRIG were significantly higher than the GMTs from the TRC-ID schedule on days 14 and 28<br>5. On day 180, subjects receiving the TRC-ID schedule had significantly higher GMTs than did the subjects receiving the 4-site ID schedule with or without eRIG; explained by the day 90 booster<br>6. The percentages of subjected who had RVNA levels > 0.5 IU/mL were not significantly different among the 3 groups from days 0 through 360 | 9.6 | 1. Schedule tested in healthy subjects<br>2. Confirmation of rabies in the biting animals in the control group was not possible | Healthy volunteers category III exposed patients from suspected rabid animals in the control group (not lab confirmed) |
| Sudarshan et al. [16] | 2012 | 1-week/4-site ID | ID | (4-4-4-0-0) | 0, 3, 7 | 3 | 0.4-0.4-0.4 (total 1.6 ml) | 7 | 80 | 1. All had no prior antirabies vaccination<br>2. The sociodemographic characteristics of the two groups were similar<br>3. Subjects were allocated randomly to PCECV or PVRV test groups | Purified chick embryo cell (Rabipur) or PVRV | 1. Blood samples were collected on days 0, 7, 14, 28, 180, and 365<br>2. All subjects in both groups had adequate RVNA concentrations > 0.5 IU/mL from day 14 to 180 and the difference of GMT between the two groups was not significant<br>3. ID booster was given to those who did not have adequate RVNA concentration on day 365 and resulted in a quick and enhanced RVNA concentrations | >2.5 | 1. Schedule tested in healthy subjects<br>2. Small sample size<br>3. Did not include vaccine combined with RIG | Healthy volunteers |

(continued on next page)



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**Table 3** (*continued*)

| Author | Year | Schedule | Route | Sites | Days | Clinic Visits | Total Dosage (mL) | Duration (days) | Sample Size | Sample Specifics | Vaccine Used | Serology Results | Potency (IU/mL) | Limitations and Concerns | Exposure characteristics |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Warrell et al. [19] | 2008 | 1 month/modified 4-site ID | ID | (4-0-2-0-1) | 0, 7, 28 | 3 | 0.4-0.2-0.1 (total 0.7 ml) | 28 | 254 | 1. The characteristics of subjects in each group were similar<br>2. Subjects received one of four PEP schedules the 2-site TRC ID, the 8-site ID (0.05 ml/site), the modified 4-site ID, or standard 5-dose IM<br>3. All had no prior antirabies vaccination | PVRV | 1. RVNA responses were measured on days 0, 7, 14, 90, and 365<br>2. All ID schedules showed similar immunogenicity<br>3. The IM schedule gave the lowest GMTs<br>4. On day 14, all subjects had antibody levels > 0.5 IU/mL<br>5. The 4-site PEP schedule is supported as immunogenic as current regimens | 5.3–8.4 | 1. Regimen tested in healthy subjects<br>2. Did not included vaccine combined with RIG<br>3. Day 90 dose | Healthy volunteers |
| Quiambao et al. [21] | 2008 | 1 month/modified 4-site ID | ID | (4-0-2-0-1) | 0, 7, 28 | 3 | 0.4-0.2-0.1 (total 0.7 ml) | 28 | 339 | 1. The characteristics of subjects in each group were similar<br>2. Subjects received one of four PEP schedules the 8-site ID no RIG, modified 4-site ID no RIG, 2-site ID TRC with RIG, or a 5-dose Essen IM without RIG<br>3. All had no prior antirabies vaccination | PVRV | 1. RVNA responses were measured on days 0, 5, 7, 14, 28, before the booster at 1 year and 2 weeks after the booster<br>2. By day 14, all subjects in the 8-site ID and modified 4-site ID groups had antibody levels > 0.5 IU/mL, 1 patient each for the other groups did not show a titre > 0.5 IU/ml<br>3. The GMT of all groups on day 14 was above 0.5 IU/mL, the modified 4-site regimen showed GMTs slightly above the TRC, but this was not statistically significant<br>4. Although the 8-site ID regimen resulted in higher antibody titres than the other 3 groups, seroconversion did not occur any earlier<br>5. The 4-site PEP schedule is supported as immunogenic as current regimens | ≥5 IU/mL | 1. Regimen tested in healthy subjects<br>2. Did not included vaccine combined with RIG for investigational regimen (modified 4-site)<br>3. Day 90 dose<br>4. Non-peer-reviewed journal | Healthy volunteers category I and II patients exposed to healthy animals |

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| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ambrozaitis et al. [20] | 2006 | 1 month/modified 4-site ID | ID | (4-0-2-0-1) | 0, 7, 28 | 3 | 0.4-0.2-0.1 (total 0.7 ml) | 28 | 180 | Healthy volunteers were randomized to receive a modified 4-site regimen with either 0.1 ml dose per injection site of PCECV or PVRV | Purified chick embryo cell and PVRV | 1. RVNA responses were measured on days 0, 7, 14, 90, and 104<br>2. By day 14, all 173 subjects reached RVNA titres above 0.5 IU/mL<br>3. For 171 of the 173 subjects RVNA titres remained above 0.5 IU/mL throughout the study with a trough on day 90 when the last ID dose was given | PCECV 5.53 IU/ml, PVCV 17.86 IU/ml | 1. Regimen tested in healthy subjects<br>2. Did not included vaccine combined with RIG<br>3. Day 90 dose | Healthy volunteers |
| Tarantola et al. [28], | in press | 1 week 2-site ID 'IPC regimen' | ID | (2-2-2-0-0) | 0, 3, 7 | 3 | 0.2-0.2-0.2 (total 0.6 ml) | 7 | 2,805 | 255 patients of the IPC rabies clinic who sought 3 and 2,497 who sought $\geq 4$ sessions of the updated TRC PEP schedule (53 received < 3 sessions). Category III exposure in 60 and 648 patients who sought 3 and $\geq 4$ sessions of the TRC PEP regimen, respectively, including confirmed rabies exposure in 90 and 1112 patients, respectively | PVRV | no immunogenicity data | $\geq$2.5 IU/mL | 1. Clinical outcome, no serology | 1066 patients with category III bites/exposures from probable rabid animals, no active follow up<br>1739 patients with category III bites/exposures from probable rabid animals, active follow up >6 months |







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systemic reactions in this study was comparable to that of rates reported for WHO approved schedules.

Overall, the safety and immunogenicity results for the 1-week, 4-site ID schedule are consistent across studies when either PVRV or PCECV are used. Compared to the updated TRC schedule this schedule reduces the number of clinic visits to 3 over a single week.

*3.1.2. 1-week IM schedule (2-0-1-0-0)*

Huang et al. 2014 evaluated the immunogenicity and safety of a one-week IM schedule compared to the 5-dose Essen IM schedule in healthy, non-rabies exposed veterinary students aged 19–23 years [18]. No RIG was administered. The 1-week IM schedule demonstrated the same immunogenicity and safety profile as the 5-dose Essen schedule, eliciting RVNA concentrations ≥0.5 IU/ml from day 14 onwards until day 180. The use of this schedule could reduce patients' expenditure, and potentially improve PEP compliance rates through fewer (2) clinic visits and a shorter course (7 days). Moreover, this schedule utilizes only three injection sites and is likely to reduce the frequency of adverse events. However, Huang et al. concluded that further investigations are necessary to continue to assess the immunogenicity and clinical effectiveness of this schedule before making new policy recommendations to change the current immunization protocols.

*3.1.3. Indirect evidence, 1-week IM schedule (1-1-1-0-0)*

In view of the lack of additional studies on investigational IM PEP schedules, indirect evidence was used to evaluate the abridgment of the 4-dose Essen IM schedule to 3 visits and 3 doses (days 0, 3 and 7). Immunogenicity data that compared investigational schedules to the IM Essen schedule showed adequate antibody titres after the third dose. Warrell et al. [19] for example included the comparative immunogenicity data of the 5-dose Essen IM regimen for days 7 and 14. GMTs for all study arms were similar and ≥0.5 IU/ml on day 14. Nevertheless, clinical outcome data to support a 1-week, 3-dose IM regimen were not available.

*3.1.4. 1-month, modified 4-site ID schedule (4-0-2-0-1)*

Ambrozaitis et al. [20] conducted a two-arm study in Lithuania comparing the modified 4-site ID schedule with a 5-session vaccine regimen: 4-site ID administration on day 0, 2-site on day 7 and 1-site on days 28 and 90. Study participants were healthy, non-rabies exposed individuals receiving either PCECV (n = 91) or PVRV (n = 89). By day 14 all study participants had RVNA titres ≥0.5 IU/ml and 99% remained ≥0.5 IU/ml until day 90. Equivalent immunogenicity of PCECV versus PVRV use for this schedule was demonstrated on day 14 and day 90, as geometric mean antibody titres (GMT) were similar for these WHO pre-qualified vaccines used.

Warrell et al. evaluated the modified 4-site ID schedule in a multi-arm, randomized controlled trial involving a total of 254 healthy, non-rabies exposed individuals [19]. The trial used PVRV in all study arms: (1) modified 4-site ID schedule (4-0-2-0-1-1) (n = 60); (2) 8-site ID schedule (8-0-4-0-1-1) (n = 65), but with an ID dose of 0.05 ml per site; (3) 2-site ID TRC schedule (2-2-2-0-1-1) (n = 66); and (4) 5-dose Essen IM schedule (1-1-1-1-1) (n = 63). All participants (100%) had RVNA concentrations ≥0.5 IU/ml by day 14.

Quiambao et al. 2008 conducted a study in 339 healthy individuals and patients who consulted for category I or II exposures to non-rabid dogs or cats in the Philippines [21]. The study included 4 arms and used PVRV: (1) 8-site ID schedule (n = 96); (2) modified 4-site ID schedule including the day 90 dose (n = 96); (3) 5-dose Essen IM (n = 97); and (4) TRC schedule (plus eRIG or human rabies immunoglobulin IM) (n = 99). All subjects (100%) had RVNA titres ≥0.5 IU/ml by day 14. The GMT of all groups on day 14 was ≥0.5 IU/ml, with the GMT of arm (1) (8-site ID) significantly higher than all other groups on day 7. The other study arms showed similar GMTs on day 14. After 1 year, the GMT of arm (1) was significantly higher than in all other groups, and results from arms (2), (3) and (4) were comparable, with 79–85% of individuals still showing titres of >0.5 IU/ml).

Compared to the TRC schedule, the modified 4-site ID schedule requires fewer clinic visits, potentially reduces vaccine wastage in small clinics and study authors claim a wider margin of safety, if the patient does not return after the first session (clinical data not available). In 2007, WHO recommended abandoning the day 90 dose of the TRC and of the modified 4-site ID schedule thereby reducing the schedules' duration to 28 days [29].

*3.1.5. 1-week, 2-site ID (2-2-2-0-0)*

A prospective study was conducted with systematic call-back starting in 2013 of all patients managed at Institut Pasteur Cambodge (IPC) between 2003 and 2014 for a bite by a category III exposure to a dog with confirmed or suspected rabies [28]. The study included 1739 eligible participants of all ages with a category III exposure to laboratory-confirmed rabid dogs and 1,066 patients bitten by untested but sick-looking dogs. All patients starting PEP received the updated TRC schedule (PVRV) including RIG. Clinical outcomes were comparable among those who completed the recommended schedule and those who terminated the protocol early, after one week/3 sessions, of their own accord. These conclusions are supported by preliminary serological outcome data from another IPC study in patients with confirmed rabies exposure (Borand et al., manuscript submitted, results partially available in [14]).

*3.1.6. Evidence on PEP schedules for special populations*

Only three recent studies were available which specifically assess rabies PEP schedules in immunocompromised individuals. Rahimi et al. [22] found that both immunocompetent and immunocompromised patients responded similarly to a 5-dose Essen IM schedule. Although the average antibody titres were higher in immunocompetent participants, the GMT ranges overlapped and were ≥0.5 IU/ml in both groups, suggesting that the immune responses were comparable.

Tanisaro et al. [23] evaluated the 5-dose TRC-ID schedule in haemodialysis patients with end-stage renal failure. All subjects (n = 14) had adequate antibody responses against rabies 14 days post vaccination. These results suggest that ID rabies vaccine administration is immunogenic in haemodialysis patients.

Sirikwin et al. [24] tested the immunogenicity of an 8-site ID regimen (8-8-8-8-8) in 27 HIV-infected patients. Both, patients whose CD4+ cell counts were below (n = 9) and above 200 cells (n = 18) per ml, were included. All had adequate antibody titres ≥0.5 IU/ml on day 14 after immunization with PCECV. There was no statistically significant difference in titres between persons with CD4+ cell count above or below 200 up to day 360. Sirikwin concluded that the 8-site ID regimen may represent an immunogenic option for HIV-infected patients with CD4+ cell counts below 200. Anecdotal experiences denote additional rabies PEP schedules that may be indicated in the above risk groups.

A study conducted in China among pregnant women with suspected rabies virus exposures found both PVRV and PCECV rabies vaccines to be safe for use in pregnant women, with no rabies cases reported in any subjects or their newborns [25]. Two recent reviews on or with reference to rabies vaccines and pregnancy are available [30,31]. The 2010 WHO position recommended that any PEP schedule for healthy persons can be used during pregnancy.

Please cite this article as: J. Kessels, A. Tarantola, N. Salahuddin et al., Rabies post-exposure prophylaxis: A systematic review on abridged vaccination schedules and the effect of changing administration routes during a single course, Vaccine, https://doi.org/10.1016/j.vaccine.2019.01.041

**Table 4**
Rabies virus neutralizing antibody titres following.

*(a) Change in route of administration during the same PEP course. Results table adapted from Ravish et al., 2014 [26]*

| Day | Switch from intradermal route to intramuscular route or vice versa | | |
|---|---|---|---|
| | Geometric mean titre | 95% CI | Range |
| 14 | 14.83 | 13.58–15.63 | 7.5–22.5 |

*(b) Change in route of administration for booster vaccination (days 0 and 3). Results table adapted from Sudarshan et al., 2006 [27]*

| Day | Intradermal route* | | | Intramuscular route† | | |
|---|---|---|---|---|---|---|
| | Geometric mean titre | 95% CI | Range | Geometric mean titre | 95% CI | Range |
| 0 | 0.59 | 0.50–0.68 | 0.5–0.8 | 0.59 | 0.50–0.71 | 0.5–1.0 |
| 14 | 8.84 | 7.58–10.30 | 7.4–12.4 | 9.17 | 7.84–10.70 | 6.9–12.7 |

* Previous vaccination by intramuscular route † previous vaccination by intradermal route CI confidence interval.
† Value for test of significance of geometric mean titre between days 0 and 14 was 79.26 for the intradermal and 24.87 for the intramuscular group. The degrees of freedom were 9 and p value < 0.0001 for both the groups.

### 3.2. Changing route of administration during a single PEP course

Although the practice of changing product or administration route during a single PEP course probably occurs, there were only two recent studies which assessed associated immunogenicity data [26,27].

Ravish et al. provided supporting evidence that changes in vaccine product (n = 43) or the route of administration (n = 47) of rabies vaccines (n = 24 from ID to IM and n = 23 from ID to IM) are safe and immunogenic [26]. All participants had antibody titres ≥0.5 IU/mL on day 14 post-immunization. Detailed immunogenicity data are available in Table 4.

In a slightly different context Sudarshan et al. conducted a study in 20 volunteers who previously received a full course of PEP [27]. The immune response was assessed by mimicking PEP for previously immunized people and necessitating a change in route of administration of PCECV vaccine. It showed that these are safe and immunologically efficacious following booster vaccination, even after a change from the ID to the IM route and vice versa.

These new studies and expert knowledge suggest that restarting PEP is not necessary after switching product or administration route.

## 4. Discussion

Available evidence suggests that current PEP schedules can be reduced in duration, and in some cases also in number of doses administered while maintaining immunogenicity and effectiveness of PEP. The largest amount of published evidence supports the 1-month modified 4-site ID and 1-week 4-site ID schedules, and further research is needed on the potential for reducing dose and duration of IM schedules, i.e. to 3 doses and/or 1-week duration. However, the 1-week 2-site ID regimen is supported by compelling clinical effectiveness and immunogenicity data from Cambodia, a rabies-endemic country. Reducing the number of clinic-visits and their associated costs potentially improves patient compliance [10,28]. The 2018 WHO recommendations for ID PEP currently represent an off-label use in many countries and it will be necessary to overcome (national) regulatory issues through e.g. regional regulatory approaches to accelerate uptake of the 2018 position. However, countries have already adopted the practice of off-label and fractional dose use of other vaccines, prior to approval from national regulatory bodies [32]. Further WHO is in continuous contact with vaccine manufacturers to urge for update of package inserts which will facilitate uptake of the WHO recommendations.

Although the 1-month modified 4-site ID and 1-week, 4-site ID schedules are shown to be safe and immunogenic, they may not all be feasible to implement, or more cost-effective than the current updated TRC-ID schedule. Not everyone agrees on the tolerable and feasible number of injection sites per visit – especially in a busy rabies clinic, in small children and among female bite victims in a conservative society, and using a 4-site injection schedule may not be fully supported by clinicians in rabies-endemic countries. Of the new schedules, the 1-week, 2-site ID PEP (IPC) schedule is therefore likely to be the most acceptable and feasible to implement.

Modelling work comparing the cost-effectiveness of different PEP schedules further shows that the 1-week, 2-site ID PEP schedule has the lowest direct costs (i.e. cost of vaccine) than any other PEP schedule in clinics with ≥5 new PEP patients per month [33]. PEP schedules that use less vaccine spare cost and may also be critical to overcome vaccine shortages in settings where vaccine availability is limited, especially where patients can be pooled for injections.

In the absence of robust, direct evidence on the effectiveness of a 3-dose IM regimen and out of caution, a 4-dose Essen IM schedule on days 0, 3, 7 and the last dose between day 14 and 28 was suggested. The established Zagreb schedule is maintained.

This combined new evidence led to the endorsement of the 2018 WHO recommended PEP schedules for category II and III exposures [34], as summarized in Table 5.

Most of the included studies did not assess the safety and immunogenicity of novel PEP schedules for special populations, such as for infants, pregnant women or immunocompromised persons, such as people infected with HIV. However, the use of PEP in these subpopulations is highly relevant and was included as a priority question by the SAGE working group on rabies. Recent publications on PEP schedules in immunocompromised persons show limitations and earlier studies in HIV-infected children [35,36] did not confirm that a higher amount of antigen, such as might be achieved through administration of supplementary rabies vaccine doses, necessarily results in an adequate immune response in persons with advanced immunosuppression. Nevertheless,

**Table 5**
2018 PEP recommendations for non-previously immunized individuals of all age groups, modified from [34].

| Category II exposure | Category III exposure |
|---|---|
| Wound washing and immediate vaccination:<br>– 2-sites ID on days 0, 3 and 7<br>– OR 1-site IM on days 0, 3, 7 and between day 14–28<br>– OR 2-sites IM on day 0 and 1-site IM on days 7, 21<br>RIG is not indicated | Wound washing and immediate vaccination<br>– 2-sites ID on days 0, 3 and 7<br>– OR 1-site IM on days 0, 3, 7 and between day 14–28<br>– OR 2-sites IM on days 0 and 1-site IM on days 7, 21<br>RIG administration is recommended |

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studies on routine vaccines have shown that HIV patients undergoing antiretroviral treatment and monitoring react similarly as non-HIV infected individuals [37,38]; and that ID immunization was as immunogenic as IM vaccination in patients with low CD4 counts who received inactivated influenza vaccines [39,40]. The updated evidence further confirms that administering rabies vaccines during pregnancy is safe, effective, does not interfere with the development of the foetus or infant; and should never be withheld.

Although the same product and route of administration should be used throughout the vaccine course, in many instances it may become necessary to change the route or product. Evidence from two studies with limited sample size suggests that changes in the vaccine product and/or route of administration during the same PEP course are acceptable in unavoidable circumstances, to promote completion of the potentially lifesaving PEP schedule. The findings further add to the consensus that modern, cell culture-derived rabies vaccines are among the highest immunogenic vaccines known, regardless of administration route or vaccine type used.

Overall, the quality of available evidence on new PEP schedules, is weakened by the small sample sizes of the reviewed studies, low numbers of randomized clinical trials, large amounts of clinical data remaining unpublished and limited geographic representativeness, as most clinical trials were conducted in South and South East Asia. The authors note that this systematic review is not exempt of common bias known from other systematic reviews: Literature published in languages other than English might only be partly captured in the databases searched and there are lower numbers of publications from rabies-endemic, low-income countries. Considerations on how to assess novel PEP regimens, while respecting ethical, scientific and health economic evaluation criteria, is published in this special issue [41]. Six of the eight trials on abridged PEP schedules were conducted only in healthy volunteers and are not supported by observational data of patients with suspect or confirmed rabies exposures from animal bites. This review indicates that more studies with larger samples sizes may be needed to improve the quality of evidence. Trials conducted on the African continent would be valuable, as the per capita rabies burden in Africa is large, but rabies vaccine studies from African countries are underrepresented in the current literature.

## 5. Conclusion

The ID route of administration has been accepted and practised in many low-income countries for several decades. Several optional regimens have been studied and proposed, but these add complexity of choice for the health care giver. Hence, the 2018 WHO position attempts to simplify the regimen without compromising effectiveness. The evidence available shows that the 1-week, 4-site ID schedule [15–17], the 1-month modified 4-site ID schedule [19–21], and the 1-week, 2-site ID schedule [14,28] are safe and immunogenic. A 1-week schedule also has obvious advantages of reducing time, cost, improving adherence, and, for high throughput clinics, reducing the volume of patients by removing the 1-month dose. Rabies vaccines are safe and efficacious to use in pregnant women and should be administered using any of the recommended schedules.

Adequate immunogenicity data alone are not considered sufficient evidence when trying to reduce the number of visits or doses in a rabies PEP schedule. Considering clinical outcome data, immunogenicity, feasibility and cost-effectiveness, the 1-week, 2-site ID PEP (IPC) schedule best fulfils the above requirements and is therefore proposed as the or a new WHO-recommended schedule for ID rabies PEP [34]. As the IPC regimen is newly recommended on the basis of clinical outcome and serological data, formal clinical trial data are lacking for the moment.

An integrated vigilance system should be implemented to detect rabies deaths among PEP recipients, especially among those exposed to confirmed rabid or untested, but sick-looking dogs [41]. This will help detect breakdowns in procedure (e.g. vaccine lost, cold chain), improve safety, and facilitate research. Research on the potential for further reducing dose and duration of both, IM and ID schedules, and on the use of rabies PEP in immunocompromised individuals needs to continue. This should be based on the protocols developed describing the data and sample size needed (supported by statistical calculations) to recommend a new PEP schedule [41]. Future research on investigational PEP schedules using internationally standardized questionnaires and surveillance methods should consider clinical outcome data, but also cost-effectiveness, programmatic feasibility and acceptability to patients and clinicians.

## Acknowledgements

We acknowledge V. Suslovitch and C. Frivold for the literature search and the members of the SAGE working group on rabies for valuable discussions.

## Disclaimer

The authors alone are responsible for the views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which the authors are affiliated.

## Conflict of interest statement

The authors declare no conflicts of interest.

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