



Post-Exposure Prophylactic Vaccination against Rabies: A Systematic Review

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Abstract

Background: Post-exposure prophylaxis (PEP) is an effective method for preventing rabies, a highly fatal infection in exposed persons. Malaysia is currently using the purified Vero cell rabies vaccine (PVRV). Nonetheless, there are other commercially available vaccine types and regimens. This systematic review aimed at comparing the effectiveness of the different PEP vaccines, regimens and routes of administration among Asian populations.

Methods: We systematically reviewed the PubMed and Web of Science databases for articles reporting on the effectiveness of PEP vaccination against rabies among Asian populations between 2015 and 2019.

Results: Our search identified 11 relevant studies. Majority of study either used PCECV or PVRV type of vaccine, with different regimes and method. All are non-inferior to the other. Most of the studies recorded adequate response by Day 14 of vaccination. Nonetheless, the intradermal (ID) vaccination used minimal volume of vaccine used in all settings, thus cost less and the concurrent administration of RIG to the wound(s) doesn't affect the RVNA GMT response.

Conclusion: PCECV, using either the Essen or Zagreb regimen, might be a useful alternative for the healthy population in the context of PVRV shortage, especially during an outbreak. Use of the Zagreb or Thai Red Cross (TRC) regimens can be considered (either PVRV or PCECV), as both demonstrate good immunogenic outcomes in Asian populations.

Keywords: Rabies; Post-exposure prophylaxis; Human; Vaccine

Introduction

Rabies is a zoonosis disease caused by a virus in the family *Rhabdoviridae*, genus *Lyssavirus*, known as rabies virus (RV). Rabies is an acute neurological infection in humans and other mammals,

where dogs transmit 99% of human infection (1). The annual estimated mortality from rabies infection was 59,000 cases and involved more than 150 countries, and 95% of these cases were from



Asia and Africa (2). Infected patients experience neurological symptoms, and the disease is 100% fatal but preventable in nature (3).

The disease is preventable after one's exposed by initiating post-exposure prophylaxis (PEP) as soon as possible. PEP vaccines for rabies are either cell culture or embryonated egg-based vaccines (CCEEVs), such as purified chick embryo cell vaccine (PCECV), purified Vero cell rabies vaccine (PVRV), purified duck embryo vaccine (PDEV) and human diploid cell vaccine (HDCV) (4). These vaccines can be administered either intramuscularly (IM) or intradermally (ID) with the regimen suggested by the WHO. ID administration was introduced in 1992 (5) and reduced the cost of vaccination by up to 60%-80% compared to IM administration of the same type of vaccine (6). Generally, PEP vaccines are given to patients with Category II and III wounds along with wound cleaning and additional rabies immunoglobulin (RIG) (Category III wounds only). PVRV and PCECV are among the widely used vaccines, especially in developing countries (7).

The WHO recommends several regimens, each with varying doses and days of vaccination. For example, the 5-dose Essen regimen (1-1-1-1-1) is given on day 0, 3, 7, 14 and 28; while the 4-dose Zagreb regimen (2-0-1-0-1) is given on day 0, 7 and 21 (5). The main challenge in administering PEP vaccines is patient compliance, as multiple injections need to be delivered in 1 month. Thus, various factors are considered when selecting the vaccine type and regimen, such as the number of injections, effectiveness in achieving early protective titre and the cost incurred. The titre measured is the RV-neutralizing antibody (RVNA), with a minimum titre of 0.5 IU/mL for adequate protection to patients exposed to RV (8). For assessing the effectiveness of the PEP vaccination and regimen administered, some studies have monitored the RVNA titre for up to 1 year (9, 10) to identify which provides the maximum protection from RV infection.

The majority (59%) of rabies-related deaths occurs in Asia (11). The national recommendations on rabies vaccination across Asian countries differ; although some guidelines are closely aligned

to the WHO recommendations, adoption of the resource-saving ID administration is generally low (12). In Malaysia, rabies cases are commonly found in the states bordering Thailand, such as Perlis, Kedah and Kelantan, which is also known as the immune belt area (13). East Malaysia was historically free from rabies until the Sarawak outbreak in 2017, especially at localities bordering Kalimantan, Indonesia (13), which received much public and media attention, especially regarding the supply of rabies vaccines (14). According to the Malaysian Interim Guideline for Human Rabies Prevention and Control, rabies vaccination is limited to PEP and is not indicated for pre-exposure prophylaxis (PrEP). In Malaysia, PVRV is administered IM with a 4-dose regimen (day 0, 3, 7, 14) for previously unvaccinated people, a 2-dose regimen (day 0 and 3) for previously vaccinated people, and a 5-dose regimen (day 0, 3, 7, 14, 28) for immunocompromised patients (15).

Due to the heterogeneity of rabies vaccination recommendations across Asia (12), the present systematic review was aimed at comparing the effectiveness among the different types of PEP vaccines, regimens and routes of administration among Asian populations. This would provide a guide for resolving issues such as sourcing for suitable alternatives when facing a shortage of PVRV, especially during outbreaks, and for the adoption of ID administration to optimise the utilisation of limited resources.

Methods

Literature Search

Two databases, i.e. PubMed and Web of Science, were systematically searched for articles reporting on the effectiveness of PEP vaccination against rabies among Asian populations. PubMed and Web of Science were chosen as it has extensive coverage in medicine and the field of science. Furthermore, all the authors have a good grasp in these two databases as a result of numerous training provided by the institution affiliated to the authors. The literature review was performed according to PRISMA (Preferred Reporting Items

for Systematic Reviews and Meta-Analyses) guidelines (16) (Fig.1). The search was limited to English publications published in the last 5 years, i.e. 2015–2019, and used a combination of search strings consisting of terms used for the disease (i.e. rabies), target population (i.e. Asian), study intervention (i.e. PEP vaccination against rabies) and study outcomes (i.e. seroconversion or antibody). The complete list of search strings is pre-

sented in Supplement 1 (Not published. Readers may contact the corresponding author to get the supplementary data). All duplicated references were removed prior to the article selection. Additionally, we also checked the reference lists of published systematic reviews and meta-analysis on PEP vaccination against rabies for potentially relevant articles published in the last 5 years that could have been missed.

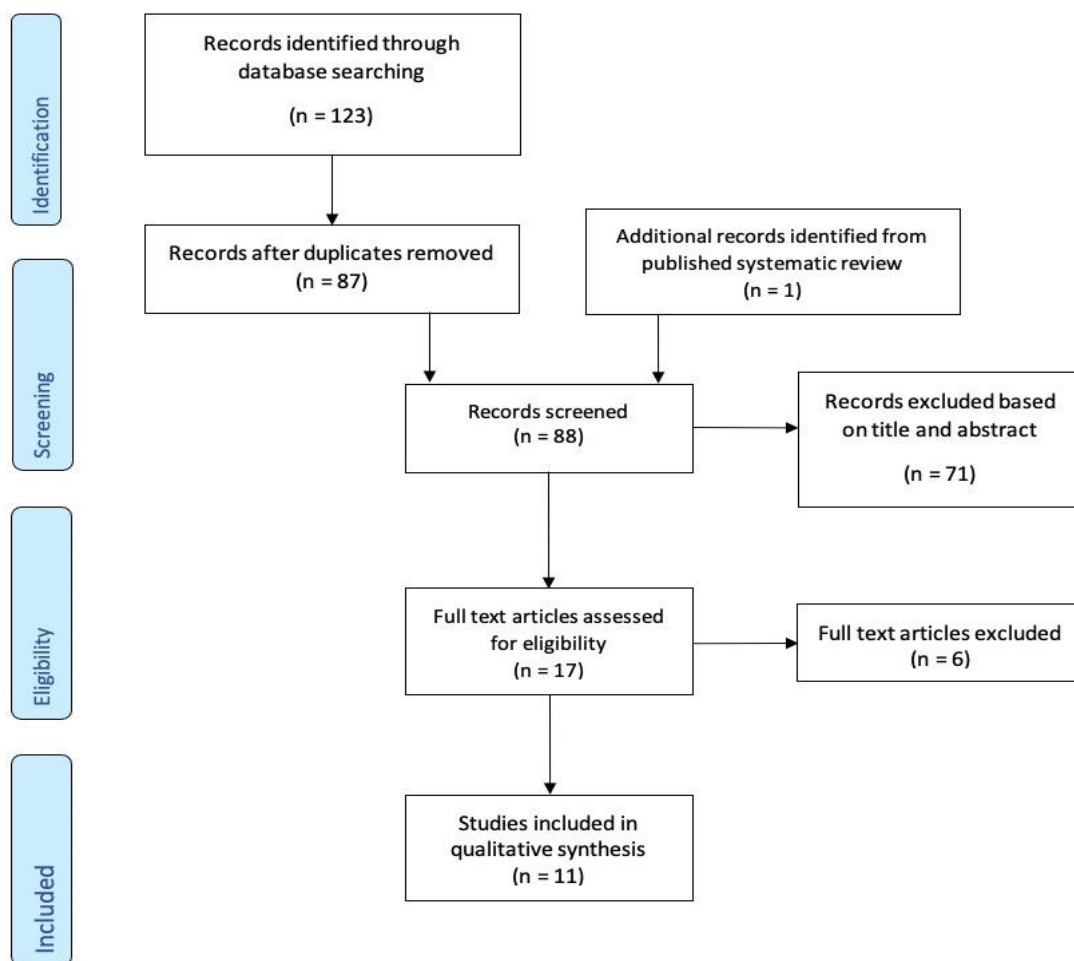


Fig. 1: PRISMA flow diagram for the studies inclusion.

Article Selection

Two researchers performed the title and abstract screening independently. All relevant articles selected by the two researchers were included in the full-text screening. The first step excluded all

articles not describing PEP vaccine for rabies among Asian populations, articles published in a language other than English, non-pertinent publication types, study protocols, conference proceedings, case reports, animal studies, articles

where the full text was not accessible, genetic studies, biochemistry or molecular studies, or modelling studies that did not provide original data. During the full-text screening, if the article answered the research question, it was then critically appraised using the Mixed Methods Appraisal Tool (MMAT) (17) (Supplement 2) (Not published). Full texts were excluded for the same reasons as those in first step, and if the article did not report quantitative data on the effectiveness of the PEP vaccine that could be retrieved from the articles. The same two researchers conducted the full-text screening and critical appraisal independently and decided on article inclusion based on consensus. If consensus could not be established, a third researcher was consulted.

Data Extraction and Analysis

Data were extracted by one researcher and were subsequently reviewed by another researcher. Standardized data extraction tables were used to summarise results by country, study design, vaccine characteristics, background of study population, administration of RIG, study outcome (e.g., immunogenicity, seroconversion) and assessment

methods. The immunogenicity- or seroconversion-related outcomes included were RVNA response in geometric mean titre (GMT) and the percentage of vaccinated individuals with adequate RVNA titres (≥ 0.5 IU/mL) at selected intervals post-vaccination. Due to the high heterogeneity of the included studies meta-analysis was not feasible.

Results

The literature search yielded 44 articles from PubMed and 79 articles from Web of Science, i.e., 123 unique hits. Only 17 articles were included in the full-text assessment after the articles had undergone rigorous selection screening (Fig. 1). Ultimately, 11 articles (Table 1) that met the objectives were eligible for the final systematic review: three from China (9, 18-19), two each from India (10,20) and Singapore (21,22) one each from Thailand (23), the Philippines (24) and Iran (8), and one that involved participants from both Thailand and the Philippines (25).

Table 1: Summary of articles included in systematic review

<i>N</i>	<i>Author (Year)</i>	<i>Country</i>	<i>Sample Size</i>	<i>Target Population</i>	<i>Study design</i>	<i>Vaccine</i>	<i>Regimen (route)</i>	<i>Results</i>
1	Bose et al. (2016)	China	182	Healthy Population	RCT: Phase II/III	C: PCECV (Rabipur) E: PVRV (Rabivax-S)	C: Essen (IM) E: Essen (IM) or TRC (ID)	Rabivax-S was well tolerated and non-inferior to Rabipur in immunogenicity for both IM and ID route.
2	Kalimudin et al. (2017)	Singapore	126	Healthy Population	RCT	C: PCECV (Rabipur) E: PIKA rabies vaccine	C: abbreviated Essen (IM) E: PIKA-accelerated (IM)	The accelerated regimen using the investigational PIKA rabies vaccine was well-tolerated and non-inferior in immunogenicity in healthy adults.
3	Kerdpanich et al. (2018)	Philippines and Thai-	885	Healthy Population	RCT: Phase III, open-label	PCECV	C: TRC (ID) E: 1-week 4-site (ID)	PCECV 1-week 4 site regimen was well tolerated and non-inferior to TRC regimen in percentage of participants with RVNA ≥ 0.5 IU/mL at

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4	Li et al. (2015)	China	640	Healthy Population	RCT: Phase IIIb, open label, age-stratified	PCECV	C: Essen (IM) E: Zagreb (IM)	day 49. The elicited immune responses peaked at day 14, and subsequently declined up to day 365. 1-week 4-site regimen might be an alternative to TRC regimen. PCECV Zagreb regimen was well tolerated and non-inferior to Essen regimen in immunogenicity with acceptable safety profile on healthy Chinese children (6-17 yr old) and older population (51 yr old and above).
5	Mahendra et al. (2015)	India	250	Healthy Population	RCT: Phase IV, open label	PCECV	C: Essen (IM) E: Zagreb (IM)	PCECV Zagreb regimen was non inferior in both immunogenicity and safety to Essen regimen by day 14 (primary endpoint), as well as day 42. Zagreb regimen might be an alternative to Essen regimen (shorter duration to increase patient compliance but equally immunogenic).
6	Narayana et al. (2015)	India	89	Healthy Population	RCT: Phase III, active controlled, parallel assigned, comparative, open label	C: PCECV (Rabipur) E: PVRV (Verorab)	Both: 1-week 4-site (ID)	There is no statistically significant difference between the RVNA GMC values for Rabipur and Verorab group.
7	Quiambao et al. (2019)	Philippines	600	Healthy Population	RCT: Phase III, single center, open label	PVRV (Verorab)	C: TRC (ID) E: 1-week 4-site (ID)	The seroconversion rate at day 14 with the 1-week 4-site regimen, both with and without RIG, was non-inferior to the reference TRC regimen with RIG on PVRV.
8	Rahimi et al. (2015)	Iran	80	Healthy population and patient	Quasi RCT	PVRV	Essen (IM) Case: patients with specific medical conditions Control: healthy population	PVRV with Essen regimen is sufficient for rabies prophylaxis in patients with specific medical conditions.

9	Shi et al. (2017)	China	552	Healthy Population	RCT	PVRV	C: Essen (IM) E: Zagreb (IM)	PVRV with Zagreb regimen had a similar safety, immunogenicity and long-term effect to Essen regimen.
10	Sirikun et al. (2018)	Thailand	58	Outpatient with history of animal bite	Quasi RCT: single center, prospective, open label	PCECV (Rabipur)	Essen (IM) Case: BMI>30k g/m ² Control: BMI<25k g/m ²	There was no statistically significant difference of RVNA GMT between two groups. There was no evidence of immunosuppression of antibodies' responses in obese patients.
11	Wijaya et al. (2017)	Singapore	37	Healthy Population	RCT: Phase I, single center, open label (1:1:1)	C: PCECV (Rabipur) E: PIKA rabies vaccine	C: abbreviated Essen (IM) E: PIKA-classic or PIKA-accelerated (IM)	The investigational PIKA rabies vaccine was well tolerated and more immunogenic than the commercially available vaccine in healthy adults.

Abbreviation:

RCT – Randomise Control Trial

C: control; E: experimental

^Include: pregnancy, diabetes, hepatitis B infection, cancer, immunocompromised: rheumatoid arthritis or lupus erythematosus.

Regimen:

Essen: (1-1-1-1) at day 0, 3, 7, 14 and 28 (IM, 1ml/dose)

Zagreb: (2-0-1-0-1) at day 0, 7 and 21 (IM, 1ml/dose)

Abbreviated Essen: (1-1-1-1) at day 0, 3, 7 and 14 (IM, 1ml/dose)

TRC: (2-2-2-0-2) at day 0, 3, 7 and 28 (ID, 0.1ml/dose)

1-week 4-site: (4-4-4-0-0) at day 0, 3 and 7 (ID, 0.1ml/dose)

PIKA-classic: (1-1-1-1) at day 0, 3, 7, and 14 (IM, 1ml/dose)

PIKA-accelerated: (2-2-1) at day 0, 3 and 7 (IM, 1ml/d)

Study Characteristics

Nine of the included studies were randomised controlled trials (RCTs), while the remaining two were quasi-experimental studies (8,23). All studies were conducted on healthy populations, except the study which recruited participants with medical conditions. Most of the studies involved adults (aged ≥18 yr), but Kerdpanich et al. recruited participants with a minimum age of 1 year, while Li et al. and Bose et al. recruited participants with a minimum age of 6 yr.

The majority of the included studies compared either PCECV or PVRV (same vaccine with different regimens) or both (different vaccine with same or different regimens). Two studies investi-

gated the effectiveness of the PIKA adjuvant vaccine (a synthetic analogue of dsRNA) (21, 22). IM administration with either the Essen or Zagreb regimen was the most commonly studied administration route, while four studies investigated ID administration, either compared against the standard IM regimen (18); among different ID regimens, i.e. Thai Red Cross (TRC) regimen versus the 1-week 4-site regimen on the same vaccine, such as PCECV (25) and PVRV (24); or different vaccines but the same regimen (10). All studies complied with the WHO rabies guideline as the standard of treatment and administered RIG in all cases with Category III exposure.

Immunogenicity

Immunogenicity was measured using RVNA GMT. Depending on the study protocol, there were multiple RVNA measurement points (i.e., day post-vaccination). All studies recorded the RVNA GMT on day 14 post-vaccination, allowing one-to-one comparison. Only three studies did not report that all participants (98.9%-99.4%) had RVNA GMT \geq 0.5 IU/mL at day 14 (19, 20, 25 days) compared the outcome between the Zagreb and Essen regimens for PVRV. All participants in the Zagreb regimen achieved RVNA GMT \geq 0.5 IU/mL at day 14, but not those on the Essen regimen (99%) (19). PCECV was examined and found that children (age 6–17 yr) achieved 100% RVNA GMT \geq 0.5 IU/mL at day 14, either on the Zagreb or Essen regimen, but the rate was 99% for the older population on the Zagreb regimen (age \geq 51 yr). The 1-week 4-site regimen was compared with the TRC regimen for PVRV and found that 100% of participants on the 1-week 4-site regimen without RIG (Category II exposure) achieved RVNA GMT \geq 0.5 IU/mL at day 14. By contrast, participants with RIG (Category III exposure) achieved 99.4% (1-week 4-site regimen) and 98.9% (TRC regimen) RVNA GMT \geq 0.5 IU/mL at day 14, respectively.

In general, all comparison groups in each study eventually achieved protective titres following PEP; the key findings are summarised below:

- a. IM administration using the Zagreb regimen was non-inferior to the Essen regimen for both PCECV (20, 21) and PVRV (9).
- b. For ID administration, the 1-week 4-site regimen was non-inferior to the TRC regimen for PCECV (26) and PVRV (24).
- c. ID administration (TRC regimen) was non-inferior to IM administration (Essen regimen) for PVRV (18).
- d. PVRV (Rabivax-S or Verorab) was non-inferior to PCECV (Rabipur) using the Essen regimen or 1-week 4-site regimen, respectively (10, 18).

e. PVRV with the Essen regimen was equally effective for patients with specific medical conditions as compared to the healthy population (8).

f. PCECV with the Essen regimen was equally effective for obese patients (body mass index $>$ 30 kg/m²) as compared with normal-weight patients (23).

g. The PIKA rabies vaccine (PIKA-classic or -accelerated regimen) was non-inferior to PCECV (abbreviated Essen regimen) (21, 22).

Rabies Immunoglobulin

Seven studies reported concomitant use of RIG in participants with Category III exposure. Four of the studies (8, 9, 18, 25) used human RIG (HRIG), while the remaining three studies (10, 23, 24) used equine RIG (ERIG). Nonetheless, the RVNA GMTs measured were similar among the participants with and without concurrent RIG administration.

Assessment Methods for RVNA Titres

Eight of the 11 included studies assessed RVNA using the rapid fluorescent focus inhibition test (RFFIT), while two studies (21, 22) used the fluorescent antibody virus neutralization test (FAVN), and one study (8) used a combination of RFFIT and enzyme-linked immunosorbent assay (ELISA). Therefore, one-to-one comparison of such findings with different assays should be performed with caution, as each assay presents different levels of sensitivity and specificity.

Quality Appraisal

Overall, the included studies were of good quality. All studies had passed the screening questions prior to inclusion by the two independent reviewers.

Discussion

This systematic review compared the effectiveness of different types of PEP vaccines and regimens among Asian populations. However, none

of them studied HDCV. HDCV has a high immunogenicity and safety profile, but it is more expensive compared to PCECV and PVRV due to the low titre of virus production, and therefore it cannot be produced on a large scale (26-28). PCECV and PVRV can achieve the desired WHO-recommended RVNA titres for adequate immune response by day 14 after initiation of the vaccine, and these findings are concordant with a study (29) and the latest the WHO position paper on rabies vaccines (28). In addition, Bose et al. (18) recorded adequate immunity even by day 1 of vaccination, as CCEEVs induce prompt and high response to RV G protein (30).

The study showed that no regimen was inferior to the others in terms of the duration needed to achieve the desired protection level. However, the variation in cost and number of injection sites between the different regimens would affect the provider's preference and patient compliance (31). ID administration only uses 0.1 mL CCEEV, which is 10%-20% of one vial of the vaccine, whilst IM uses the entire vial (32,33). The high cost of IM administration of CCEEVs inhibits the universal use of the vaccine. Hence, the WHO recommends administering CCEEVs through the ID route, as it is safe, cost-effective and dose-sparing (32,33). Further, the concentration of antigen-presenting cells in the dermis contributes to the strong immune response to the vaccine administered via the ID route (30).

Additionally, factor such as adverse effects need to be considered, as they affect patient compliance. Minor transient erythema, pain or swelling over the injection site is quite common in 35-45% of vaccinated people, especially with ID administration (32). Hence, the TRC schedule may be troublesome for the patient, as this regimen involves injecting two sites at each visit; cumulatively, the patient will receive eight injections compared to the Zagreb regimen, which only involves four injection sites over the course of three visits and a much shorter duration compared to other regimens (34). Therefore, the Zagreb regimen is more favourable for the patient compared to other regimens, especially for poor patients with limited access to health facilities,

paediatric cases and clinics with more than five rabies patients per week (35).

Except Rahimi et al., the included studies did not assess the safety and immunogenicity of the vaccines in special populations such as pregnant women and people with chronic disease (8). However, these conditions are relevant because anyone can sustain rabies dog bites. HIV patients on antiretroviral treatment responded as well to the influenza vaccine as non-HIV-infected people (36). Here, the included studies noted substantial evidence for the usage of rabies vaccines in children (9, 18, 25), except for the infant population. This limits the applicability of the vaccines for the infant population.

In most cases, thorough wound washing with prompt and complete PEP vaccination is highly effective for patients, with >99% survival (32). The WHO recommends administering RIG only for Category III transdermal wounds in unimmunised people (28). Both types of RIG, either ERIG or HRIG, are equally effective (37). Concurrent RIG administration has limited impact on vaccine effectiveness (38). Therefore, the included studies observed similar immunogenicity outcomes among participants with and without concurrent RIG administration.

The included studies used three main types of assays (i.e. RFFIT, FAVN, ELISA). As each assay has different sensitivity and specificity, this limits the comparability between the included studies. For example, FAVN has low sensitivity compared to RFFIT because the virus-neutralizing antibody appears around 1 week after clinical symptoms appear. ELISA is preferred over FAVN because it is easier to perform and has similar detection capacity as FAVN (32).

Overall, there were no differences in term of effectiveness and immunogenicity among the types of vaccines (i.e. PCECV, PVRV, PIKA), regimens and doses, and routes of administration (IM versus ID). This is in line with the WHO prequalification requirement of each human rabies vaccine supplied through United Nation agencies, in which vaccine quality, safety and efficacy as well as the suitability of its usage globally is verified (32). The two most promising regi-

mens are the Zagreb regimen (2-0-1-0-1) and TRC regimen (2-2-2-0-2); the former would benefit patients more, whilst the latter benefits health facilities because it is more cost-effective. Nevertheless, it is in line with the WHO recommendation based on the latest evidence (28). However, further research needs to consider immunocompromised and chronic patients, as they might have different biological reactions to the vaccine compared to healthy people, thus impairing the effectiveness and immunogenicity through the enhanced surveillance system. Vaccine safety and patient acceptability should be considered as well. In Malaysia, PVRV with the abbreviated Essen regimen (for previously unvaccinated people) and the Essen regimen (for immunocompromised patients) is utilised (15). PCECV might be a useful alternative for the healthy population in the context of a PVRV shortage, especially during an outbreak, using either the Essen or Zagreb regimen. Adoption of the Zagreb or TRC regimen can also be considered (either PVRV or PCECV), as both demonstrate good immunogenic outcomes among Asian populations, as illustrated in this review. Although the ID regimen is more cost-saving and with an equally good immunogenic and safety profile, it nonetheless involves more injection sites; therefore, it is important to evaluate its acceptability among the Malaysian population before adopting it as routine practice. By contrast, adoption of the Zagreb regimen is relatively easier, as it is more similar to the current practice, either to the public or to health care personnel.

Conclusion

Based on the data presented above, we conclude that post-exposure prophylactic against rabies of any vaccination regime is safe and efficacious to mount good immune response. Therefore, we encourage the health practitioners to provide the rabies vaccine to susceptible patients that come to seek treatment.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interests

The authors declare that they have no competing interests.

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