INTRADERMAL (ID) INJECTION OF RABIES VACCINE: POST-EXPOSURE (PEP) AND PRE-EXPOSURE (PrEP) PROPHYLAXIS & ECONOMIC EVALUATION

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INTRADERMAL (ID) INJECTION FOR RABIES VACCINE: POST-EXPOSURE (PEP) AND PRE-EXPOSURE (PrEP) PROPHYLAXIS & ECONOMIC EVALUATION

EXECUTIVE SUMMARY

BACKGROUND

Rabies is an acute encephalitis which is highly fatal old zoonotic disease caused by a bullet-shaped Lyssavirus. This disease now kills more than 69,000 people every year mostly in Asia and Africa. Rabies was eradicated from Malaysia in 1999 after the last human case in 1998 and last dog case in 1999 prompting the World Association for Animal Health to declare Malaysia rabies free in 2012 and since then there was no major outbreak until the recent outbreak. The outbreak started in July 2015 in Perlis.

Transmission of rabies virus (RABV) by dog is responsible for up to 99% human rabies cases in rabies-endemic regions, with small proportion due to transmission via wildlife (foxes, wolves, jackals, bats, racoons, skunks or mongoose). Rabies prevention and control consists of different methods including wild and domestic animal vaccination programs, animal birth control, responsible pet ownership and rabies education and awareness. Human rabies vaccination is one of the most important elements of preventing rabies in humans. World Health Organisation (WHO) recommend two main immunization strategies which are pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP).

According to current report from WHO, vaccine potency showed that current vaccines (≥2.5 IU/IM dose), when administered by intradermal (ID) route for either PEP or PrEP, have efficacy equivalent to or higher than the same vaccine administered by intramuscular (IM) route. For the ID route one dose is 0.1 mL of rabies vaccine (irrespective of the vaccine brand). The vaccine in one vial can therefore be fractionated to provide five to ten doses for ID administration, depending on the vial size (0.5 mL or 1.0 mL). In 1992, WHO approved it for use in developing countries which face a shortage of rabies vaccine due to paucity of funds. For the IM route one dose is one vial of vaccine per patient. However, the current route of administration in the rabies vaccine leaflet is IM not ID, hence it has been used off-label. Compared to IM recommended schedule, the ID schedules offer advantages through savings in costs, doses and time. Head of Zoonosis Sector of Disease Control Division requested further assessment on ID rabies vaccine injection given as PrEP and PEP.

OBJECTIVES/AIMS

1. To assess and compare the safety, efficacy/effectiveness, cost-effectiveness and organizational issue of ID and IM rabies vaccine for PEP and PrEP.
2. To compare the cost of IM and ID post-exposure and pre-exposure rabies vaccine

RESULTS & CONCLUSION

Part A (Systematic Review)

There were fair to good level of evidence retrieved on ID rabies vaccine. Out of seven included studies in this technology review, two systematic review (SR) and meta-analysis (MA), 1 non RCT and 1 non-blinded RCT compared ID routes and IM routes of rabies vaccine. Whereas other studies (two RCTs and 1 pre- and post-intervention study) compared different regimes and schedule of intradermal rabies vaccine. Two studies were on PEP and the other five studies were on PrEP.

Efficacy / Effectiveness

Pre-Exposure Prophylaxis (PrEP)
Comparing PrEP by ID route and IM route, both routes achieved seroconversion and the Rabies Virus Neutralizing Antibodies Geometric Mean Concentrations (RVNA GMTs) were above the desired level. However, the RVNA GMTs in IM route was significantly higher than ID route. After booster dose, both routes showed rapid increase in virus neutralizing antibody GMTs (above the desired level). However, the GMTs level in IM route was significantly higher than in ID route.

One study showed that high seroconversion rate after one month of single visit of PrEP rabies vaccination with ID route. However, after one year the RVNA GMTs declined and was later increased with first booster dose. The seroconversion was also completed within one week of the first booster dose. The seroconversion rate and the RVNA GMTs was higher in IM route compared to the ID route.

For PrEP with ID rabies vaccine at different schedule and regimes, more patients with 2ID regime achieved GMT level ≥ 0.5 IU/ml and ≥ 10 IU/ml after one- or three-years primary vaccination schedules compared to 3ID regimes. On the other hand, one study reported that 4-site/1-week schedule and standard regimen of Thailand Red Cross (TRC) (2-site/TRC) schedule achieved the same adequate RVNA GMT level of ≥ 0.5 IU/ml. However, the immune response at day 365 was higher in 4-site/1-week regimen than 2-site/ Thai Red Cross (TRC) regimen.

As for the Rabies Immunoglobulin (RIG) administration, when comparing 2-site ID TRC regimen with or without RIG, both regimes reached adequate immune response in WHO categories II and III paediatric patients on day 14 and day 90.

Post Exposure Prophylaxis (PEP) Rabies Vaccination
After primary and booster vaccination of PEP, both routes either IM or ID achieved seroconversion rates and the RVNA GMT level of ≥0.5 IU/ml. Both levels were higher in IM route compared to ID route.

Safety

Currently, no rabies vaccine via ID route is approve by United State Food and Drug Administration (USFDA) and the use of ID rabies vaccine in US remained off-label.

The most common adverse events (AEs) of rabies vaccine when comparing ID route and IM route can be divided into local AEs and systemic AEs. Compared with IM route, erythema, induration and lymphadenopathy were reported more frequently in ID route.

When comparing 3-ID schedule and 2-ID schedule, serious AEs which included reversible diplopia and hemianopsia occurred during final dose of primary vaccination of 3-ID schedule while oesophagitis with dyspnea, angioedema and urticarial occurred during booster dose of 2-ID schedule. For non-serious AEs, local irritation at the injection site during primary vaccination occurred more frequently in 3-ID schedule compared to 2ID schedule. However, during booster local irritation occurred more often in 2-ID schedule. Systemic AEs was very low in both schedule and not significant.

Referring to pre- and post-intervention study of ID rabies vaccine in paediatrics patients, more local irritations at ID injection sites such as local erythema, induration, pain and itching which were self-limiting within two days and no treatment were required. Others AEs were myalgia and fevers.

Cost/Cost-Effectiveness Analysis

No cost-effectiveness analysis retrieved
No local cost analysis was retrieved.

Organizational

Ministry of Health Malaysia has come out with Interim Guideline for Human Rabies Prevention and Control in Malaysia while Sarawak state had developed Sarawak Plan of Action for Rabies Elimination by 2020.

The ID route techniques requires skills and if the bleb does not appear during the injection, the particular dose of the rabies vaccine must be repeated.

Part B (Cost Analysis)

Five scenarios were constructed, where Scenario 1 was a base-case. The base-case scenario is a scenario that using data provided based on a current practiced. Scenario 2 to Scenario 5 referred to several situations which probably might applied during practice. Scenario 2 was a scenario where 50% of vaccinated persons will receive IM and another 50% will receive ID route of rabies vaccine. Scenario 3 was a scenario where all vaccinated persons receive ID route Rabies vaccine and all vaccinated persons in Scenario 4 receive IM route of rabies vaccine. Scenario 5 was a scenario where the used of rabies vaccine per vial will be optimised; one vial of rabies vaccine 0.5ml/vial was maximised for two persons. The analyses will discuss further based on the total cost of vaccination per year which already included cost in Sarawak and Perak region. Listed below were the cost saving (percentage difference) among various scenarios compared.

i) *Scenario 1 versus Scenario 2*: Scenario 2 reduced 4.07% of total rabies vaccination cost per year
ii) *Scenario 1 versus Scenario 5*: Scenario 5 reduced 32.94% of total rabies vaccination cost per year
iii) *Scenario 2 versus Scenario 4*: Scenario 2 saved 14.29% than Scenario 4

iv) *Scenario 3 versus Scenario 4*: Total cost saving of rabies vaccination was more in Scenario 3 (25%)
v) *Scenario 4 versus Scenario 5*: Optimum used of rabies vaccine per vial with ID route saved about 38.83% compared to only IM route (Scenario 4)

CONCLUSION

Based on the CMA, ID route of rabies vaccine either for PEP or PrEP was cost-saving compared to IM route. The optimum used of ID routes of rabies vaccine (one vial of rabies vaccine 0.5ml/vial was maximised for two persons) will save more compared to the base case (Scenario 1) especially during outbreak with a cost saving of approximately 32.94%.

RECOMMENDATION

Based on the above review, rabies vaccine administration through intradermal route is recommended during outbreak and prophylaxis as it may reduce the cost approximately at 32.94%. However, the intradermal technique requires prior training.

METHODS

Part A
Electronic databases were searched through Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present, EBM Reviews-Cochrane Database of Systematic review, EBM Reviews-Cochrane Methodology Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-NHS Economic Evaluation Database, and Embase 1996 to 10 Januari 2019. Searches were also run in PubMed, FDA website and International Network of Agencies for HTA (INAHTA) for any published reports.

No limit in the study year. Google and Google Scholar were also used to search for additional web-based materials and information about the technology. Besides, additional articles were also search by reviewing the references of retrieval articles.

Part B
Cost-minimization analysis (CMA) was conducted from the healthcare system perspective. The CMA of comparing an intradermal route of rabies vaccine against intramuscular route was performed. The model was a direct calculation which was developed based on available local data and was created in a spreadsheet (Excel 2010, Microsoft Corporation). The model provides the Disease Control Division an opportunity to include their own direct costs and reimbursements amounts from any specific payer to arrive at real-time values.

INTRADERMAL (ID) INJECTION FOR RABIES VACCINE: POST-EXPOSURE (PEP) AND PRE-EXPOSURE (PrEP) PROPHYLAXIS

1. BACKGROUND

Rabies is an acute encephalitis which is highly fatal old zoonotic disease caused by a bullet-shaped Lyssavirus.[1]The virus is capable of affecting all warm blooded mammals with mortality reaching almost 100% after onset of clinical signs or symptoms. This disease now kills more than 69,000 people every year mostly in Asia and Africa. Rabies was eradicated from Malaysia in 1999 after the last human case in 1998 and last dog case in 1999 prompting the World Association for Animal Health to declare Malaysia rabies free in 2012 and since then there was no major outbreak until the recent outbreak. The outbreak started in July 2015 in Perlis.[2]

Transmission of rabies virus (RABV) by dog is responsible for up to 99% human rabies cases in rabies-endemic regions, with small proportion due to transmission via wildlife (foxes, wolves, jackals, bats, racoons, skunks or mongoose). Rabies virus can be found in saliva, tears, urine and nervous tissue of human rabies cases and exposure to these body fluids and tissues carries a theoretical risk of transmission. Rabies virus is not found in the blood.[1]

Rabies prevention and control consists of different methods including wild and domestic animal vaccination programmes, animal birth control, responsible pet ownership and rabies education and awareness. Human rabies vaccination is one of the most important elements of preventing rabies in humans.[3] World Health Organisation (WHO) recommend two main immunization strategies which are pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) for the prevention of human rabies:[1,3]

i. PEP: Includes extensive and thorough wound washing at the RABV-exposure site, together with rabies immunoglobulin (RIG) administration is indicated, and the administration of a course of several doses of rabies vaccine;
ii. PrEP: Administration of several doses of rabies vaccine before exposure to RABV. The WHO recommend PrEP for individuals at high risk of RABV exposure which include sub-populations in highly endemic setting with limited access to timely and adequate PEP, individuals at occupational risk, and travellers who may be at risk of exposure. The decision to implement a population-based PrEP intervention should be based on assessment of the local context and rabies epidemiology, including the feasibility of controlling rabies in the animal source.

According to WHO, an estimated 35,172 human deaths (59.6% of global deaths) and loss of approximately 2.2 million disability-adjusted life years (DALYs) occur per year in Asia due to dog-mediated rabies where India accounts for the most deaths in Asia (59.9% of human rabies deaths) and globally (35% of human rabies deaths).There was use of nerve tissue vaccines in Bangladesh, Myanmar and Pakistan; however, their use has been discontinued in these countries since 2011, 2013 and 2015, respectively. The cost of PEP is highest in Asia, with estimates up to US$ 1.5 billion per year. Despite widespread underreporting and

uncertain estimates, rabies is a major burden in Asia, particularly for the rural poor. The number of human deaths globally due to dog-mediated rabies is estimated to be 59,000 annually, with an associated loss of 3.7 million DALYs. The majority of deaths occurred in Asia (59.6%) and Africa (36.4%), and most DALYs were due to premature death (> 99%) and a few to adverse events after administration of nerve tissue vaccines (0.8%). The overall economic cost of dog-mediated rabies was estimated in a probability decision-tree model to be US$ 8.6 billion (95% CI, 2.9, 21.5 billion).[4]

Since 1983, countries in the WHO Region of the Americas have reduced the incidence of rabies by over 95% in humans and 98% in dogs. This success has been achieved mainly through the implementation of effective policies and programs that focus on regionally coordinated dog vaccination campaigns, raising public awareness, and widespread availability of PEP. Many countries in the WHO South-East Asia Region have embarked on rabies elimination campaigns in line with the target of regional elimination by 2020. Bangladesh launched an elimination programme in 2010 and, through the management of dog bites, mass dog vaccination, and increased availability of vaccines free of charge, human rabies deaths decreased by 50% between 2010 and 2013. Great strides have also been made in the Philippines, South Africa and the United Republic of Tanzania where proof of concepts, as part of a Bill & Melinda Gates Foundation project led by WHO, recently showed that a reduction in human rabies cases is possible through a combination of interventions involving mass dog vaccination, improved access to PEP, increased surveillance and raising public awareness.[5]

According to Interim Guideline for Human Rabies Prevention & Control in Malaysia by the Disease Control Division, Ministry of Health (MOH), general guideline for dog bite management according to category of exposure that determines the indicated PEP procedure is as follows:[6]

- Category I: Touching or feeding an animal or licks on intact skin: no exposure; PEP not indicated;
- Category II: Nibbling of uncovered skin, minor scratches or abrasions without bleeding: exposure; PEP indicated with vaccine; to be treated as category III if exposure was to a bat; and
- Category III: Single or multiple transdermal bites or scratches, contamination of mucous membranes with saliva from licks, licks on broken skin, exposure due to direct contact with bats: severe exposure

In Malaysia, based on the interim guideline, PEP management is practiced. The treatment will be delivered as soon as possible after exposure to prevent the onset of symptoms and death. The PEP prophylaxis consist of local treatment of the wound, administration of rabies immunoglobulin (RIG) if indicated and immediate vaccination (PEP). The vaccine is administered via intramuscular (IM) only and the dose required is determined by previous immunization of the individual (refer section 3.31).[6]

According to current report from WHO, vaccine potency showed that current vaccines (≥2.5 IU/IM dose), when administered by intradermal (ID) route for

either PEP or PrEP, have efficacy equivalent to or higher than the same vaccine administered by IM route. For the ID route one dose is 0.1 mL of rabies vaccine (irrespective of the vaccine brand). The vaccine in one vial can therefore be fractionated to provide five to ten doses for ID administration, depending on the vial size (0.5 mL or 1.0 mL).[1] In 1992, WHO approved it for use in developing countries which face a shortage of rabies vaccine due to paucity of funds. For the IM route one dose is one vial of vaccine per patient.[10] However, the current route of administration in the rabies vaccine leaflet is IM not ID, hence it has been used off-label. Compared to IM recommended schedule, the ID schedules offer advantages through savings in costs, doses and time.[1] Head of Zoonosis Sector of Disease Control Division requested further assessment on ID rabies vaccine injection given as PrEP and PEP.

2. OBJECTIVE/AIM

1. To assess and compare the safety, efficacy/effectiveness, cost-effectiveness and organizational issue of ID and IM rabies vaccine for PEP and PrEP.
2. To compare the cost of IM and ID post-exposure and pre-exposure rabies vaccine treatment

3. TECHNICAL FEATURES

3.1 Rabies Virus

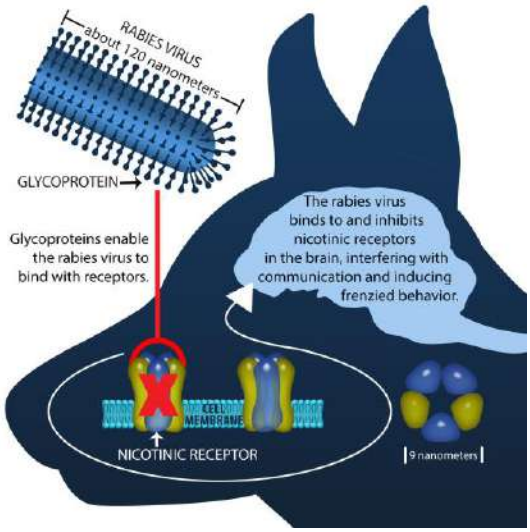

Figure 1: Rabies Virus

Rabies viruses belong to the *Mononegavirales* order, the *Rhabdoviridae* family and the *Lyssavirus* genus. There are at least 14 individual *Lyssavirus* species, subdivided into two phylogroups based on genetic distance and serological cross-reactivity. Rabies virus is unsegmented, single stranded, negative sense, enveloped RNA virus and belongs to Phylogroup-1. The genome encodes five proteins that form the functional and structural components of the virion. The ribonucleoprotein complex, essential for viral replication and protein translation, comprises nucleoprotein bound-nucleic acids, RNA-dependent RNA polymerase and phosphoprotein. The matrix and glycoproteins (G) are associated with the

host-derived lipid envelope to form the structure leading to the host cell receptor binding. The most important of these viral proteins is the G protein. The G protein includes the antigenic sites targeted by rabies vaccine-induced antibodies and RIG.[1]

3.2 Rabies

The WHO case definition for human rabies defines a human clinical case as follows; a subject present with an acute neurological syndrome (encyphalitis) dominated by forms of hyperactivity (furious rabies) or paralaytic signs (paralytic rabies) progressing towards coma and death, usually by cardiac or respiratory failure, typically within seven to ten days after the first sign. Signs and symptoms of rabies include any of the following: hydrophobia, aerophobia, photophobia, paraesthesia or localized pain, dysphagia, localized weakness, nausea or vomiting. The standard human case classification for rabies is:[1]

- Suspected: A case that is compatible with a clinical case definition
- Probable: A suspected case plus a reliable history of contact with a suspected, probable or confirmed rabid animal
- Confirmed: A suspected or probable case that is laboratory-confirmed (usually post-mortem).

3.3 Rabies Vaccines

Figure 2: Rabies Vaccine

Rabies vaccine is a vaccine used to prevent rabies. Rabies vaccine can be used to prevent rabies before exposure (PrEP) and for a period of time after exposure (PEP) to the virus (by a dog or bat bite).[7]

Human rabies vaccines include:[4]

i. Cell culture vaccines: Purified chicken embryo vaccine (PCECV), purified Vero cell vaccine (PVRV)
ii. Cell rabies vaccine and human diploid cell vaccine (HDCV)
iii. Duck embryo vaccine; and
iv. Nerve tissue vaccines: WHO recommends discontinuation of nerve tissue vaccines, because they induce severe adverse reactions and are less immunogenic than other vaccines[1,7]

According to WHO Rabies Guideline 2018, vaccines can be administered intradermal or intramuscularly.[4] The immunogenicity of the vaccine is measured

as an antibody titer. The rabies antibody titer is essentially an estimation of an immune response against rabies virus (either through exposure or vaccination). The rapid fluorescent focus inhibition test (RFFIT) is one method which provides a laboratory measurement of the ability of an individual human or animal serum sample to neutralize rabies virus.[8]

The definition of a minimally accepted antibody titer varies among laboratories and is influenced by the type of test conducted. Centres for Disease Control and Prevention (CDC) currently specifies a 1:5 titer (complete inhibition) of rabies vaccine by the RFFIT as acceptable. Meanwhile the WHO specifies a titer of 0.5 IU. The results of the RFFIT can be expressed as a serum titer or in International Units (IU) of antibody per millilitre of serum (IU/mL) which is also expressed as Geometric Mean Titer (GMT) or Geometric Mean Concentration (GMC).[9]

Generally, antibody levels are expected to be highest approximately 2-3 weeks after completing a primary rabies virus vaccination series. After being vaccinated, antibody levels subside over time. Complete neutralization of rabies virus at a serum dilution of 1:5 (~0.11 IU/mL) is recommended by the Advisory Committee on Immunization Practice (ACIP) as evidence that an individual still has a detectable level of rabies virus neutralizing antibodies (RVNA). At this level, an immune competent individual would be expected to mount a rapid response to a booster dose of rabies vaccine in the event of an exposure, precluding the need of rabies immune globulin (RIG) during PEP prophylaxis. If a person with an occupational risk of rabies virus exposure does not have evidence of RVNA at a serum dilution of at least 1:5 (~0.11 IU/mL), then they should receive a single booster dose of rabies vaccine.[8]

3.3.1 Intramuscular (IM) Rabies Vaccine

Current rabies vaccines are produced as individual doses for IM injection. The rabies vaccine reconstituted with 0.5 or 1 mL of diluent in one IM dose vial with a potency of ≥ 2.5 IU per dose can be used for both PrEP and PEP. Once opened, the vaccine vials should be stored at +2ºC to a maximum of +8ºC for no longer than six to eight hours. Rather than discarding vaccine after this time, any remaining vaccine in a vial could be used for PrEP, particularly for professionals active in animal disease control or for staff at health facilities who regularly attend to clinical rabies patients. Scheduling follow-up PrEP visits for patients within similar periods may help to minimize wastage. For IM route, the vaccine should be injected into the deltoid muscle for adults and children aged ≥ 2 years. Meanwhile, for children aged < 2 years old, anterolateral thigh is recommended.[4] Under Ministry of Health Drug Formulary, the rabies vaccine available is Verorab 1.0mL/vial.

Referring to the Interim Guideline for Human Rabies Prevention & Control in Malaysia, one dose of IM route is 1.0mL after reconstitution, depending on the type of the vaccine used. The rabies vaccination schedule is divided as follows:[6]

i) Previously unvaccinated people: Four doses at day 0, day 3, day 7 and day 14. In addition, the patient should receive a dose of RIG at the same time as the first dose of the vaccine to provide rapid protection that persists until the vaccine works

ii) Previously vaccinated people: Two doses at day 0 and day 3 and RIG is unnecessary and should not be given

iii) Immunocompromised patient: Five doses at day 0, day 3, day7, day 14 and day 28. In addition, the patient should receive a dose of RIG at the same time as the first dose of the vaccine to provide rapid protection that persists until the vaccine works

3.3.2 Intradermal Rabies Vaccine

One dose of ID route is 0.1mL of rabies vaccine, the recommended sites include the deltoids, lateral thighs or suprascapular areas that drain into lymph glands.[4] The administration of ID route require proper training to ensure the successfulness of the vaccine delivery. However, there is currently no evidence on the recommendation of a potency of 2.5 IU per IM dose and a volume of 0.1 mL per ID dose (corresponding to a potency of ≥ 0.25 IU per dose).[1,4]

The Intradermal Rabies Vaccine (IDRV) was first introduced in Thailand in 1984. The PVRV, PCECV and HDCV can be injected by the ID route for PEP as approved by WHO. The regimen approved by the WHO/Drug Controller General of India (DCGI) India is the Updated Thai Red Cross Regimen, which involves injection of 0.1 mL of reconstituted vaccine per ID site and on two such ID site per visit on Days 0, 3, 7 and 28 (number of dose administered 2-2-2-0-2).[10]

Table1: WHO-Recommended and Alternative Pre-Exposure Prophylactic Rabies Regimens

PrEP regimen	Duration of course	Number of injection sites per clinic visit (days 0, 3, 7, 14, 21–28)
WHO-recommended intradermal regimen		
Two visits	7 days	2-0-2-0-0
WHO-recommended intramuscular regimen		
Two visits	7 days	1-0-1-0-0
PrEP under specific circumstances		
Single visit, intradermal	1 day	2-0-0-0-0
Single visit, intramuscular	1 day	1-0-0-0-0

3.3.3 Mechanism of Action of Rabies Vaccine

Following ID or IM administration, rabies vaccine induces the formation of protective antibodies to rabies virus, thereby providing active immunity to rabies virus.[11]

3.5 Rabies Immunoglobulin (RIG)

Rabies immunoglobulin is a medication made up of antibodies against the rabies virus. It is used to prevent rabies following exposure. It is given after the wound is

cleaned with soap and water or povidone-iodine and is followed by a course of rabies vaccine.[12] People with category III exposure who have not received at least two doses of PrEP or PEP and severely immunocompromised people with category II exposure should receive both an effective rabies vaccine and RIG. Rabies immunoglobulins should preferably be administered into and around the wound site to neutralize the RABV still present therein. Three classes of biological product are available for passive immunization; human RIG, equine RIG and highly purified fragments produced from equine immunoglobulin. The RIG should be given with the first dose if vaccine into and around the wound site. The dose of RIG as follows:[4]

i. Human immunoglobulin: maximum dose of 20IU/kg of body weight
ii. Equine immunoglobulin: maximum dose of 40IU/kg of body weight

However, when the RIG is unavailable, thorough wound cleaning and deep irrigation with application of a potent antiseptic agent and timely administration of the first rabies vaccine dose are key factors in increasing survival.[4]

4. METHODS

4.1. Searching

Electronic databases were searched through Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present, EBM Reviews-Cochrane Database of Systematic review, EBM Reviews-Cochrane Methodology Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-NHS Economic Evaluation Database, and Embase 1996 to 10 January 2019. Searches were also run in PubMed, FDA website and INAHTA for any published reports.

No limit in the study year. Google and Google Scholar were also used to search for additional web-based materials and information about the technology. Besides, additional articles were also search by reviewing the references of retrieval articles. Appendix 1 showed detailed of the search strategies.

4.2. Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection.

The inclusion and exclusion criteria were:

Inclusion Criteria

Inclusion criteria	
Population	Rabies
Interventions	Intradermal rabies vaccine, pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP)
Comparators	Intramuscular rabies vaccine
Outcomes	Efficacy & effectiveness (immunogenicity, seroconversion), safety, cost-effectiveness, and organisational
Study design	Systematic reviews (SR), randomized controlled trials (RCT), non-RCTs, pre and post-intervention study
	English full text articles

Exclusion Criteria

Exclusion criteria	
Study design	Animal studies, laboratory studies, case reports, case series, cohort, case-control, cross-sectional study
Intervention	Other than intradermal rabies vaccine
Outcome	Non-medical condition e.g wellness, dermatology
	Non English full text article

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP), Cochrane tools, and evidence graded according to the US / Canadian Preventive Services Task Force (Appendix 2). Data were extracted from included studies using a pre-designed data extraction from (evidence table as shown in Appendix 3) and presented in tabulated format with narrative summaries. No Meta-analysis was conducted for this review.

5. RESULTS AND DISCUSSION

A total of 1,987 titles were screened and after removing duplications and studies from 1980s and 1990s, 589 abstracts were screened. Out of 589 abstracts, 576 studies were excluded because of not meeting the inclusion criteria. Thirteen full texts studies were assessed for eligibility. Out of 13 studies, seven studies were included in the report.

The included studies consisted of two systematic reviews with meta-analysis (SR and MA), three randomised controlled trials (RCT), one non-RCT and one pre and post intervention study. The characteristics of included studies were discussed in the next section. Figure 3 shows the flow chart of study selection.

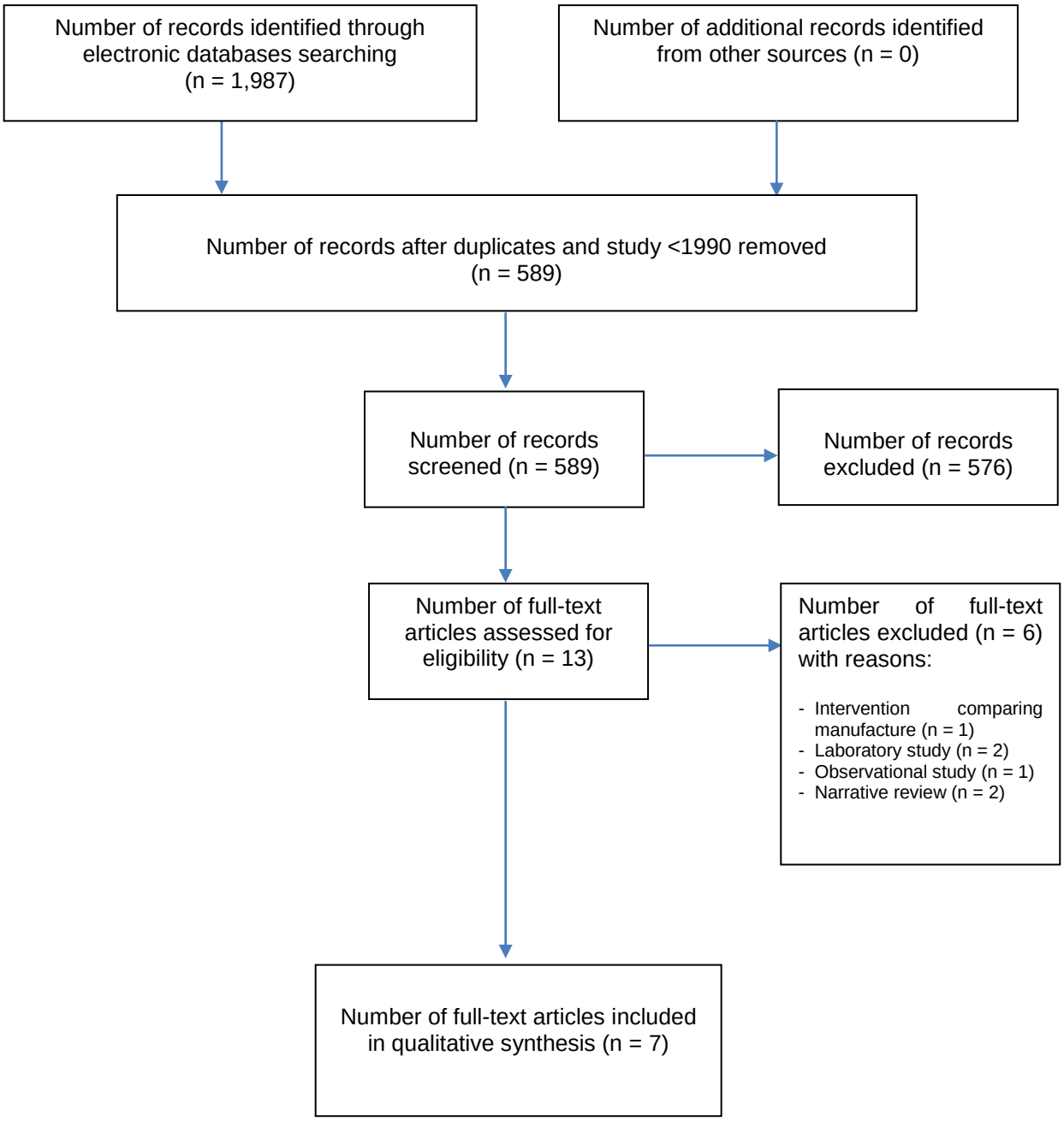

Figure 3: Flow chart of study selection

5.1 RISK OF BIAS

One of the tools that are being used by MaHTAS to assess the risk of bias is the CASP checklist which consists of eight critical appraisal tools designed for SR, RCT, cohort studies, case control studies, economic evaluations, diagnostic studies, qualitative studies, and clinical prediction rule. This is achieved by answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

+	Indicates YES (low risk of bias)
?	indicates UNKNOWN risk of bias
-	Indicates NO (high risk of bias)

Assessment Using CASP Checklist for SRs

The risk of bias of the included SRs is summarised in Figure 4 based on the Critical Appraisal Skills Programme (CASP) checklist. Two SRs were included in this assessment. Overall, both SRs fulfilled the criteria assessed accept for one SR showed that the included study were having high heterogeneity.

The results of risk of bias of included studies are summarised in Figure 4 to Figure 7.

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies included?)	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?
Langedijk AC. et al 2018[13]	+	+	+	?
Preiss S. et al 2018[14]	+	+	+	+

Figure 4: Assessment of risk of bias of Systematic Review (CASP Checklist)

Assessment Using Cochrane Collaboration's Tools for RCTs

The risk of bias for RCTs was assessed using Cochrane Collaboration's Tools. The assessment is summarised in Figure 5. Three RCTs were included and all studies did not clearly mention about allocation concealment which may lead to other possible bias. Besides, no blinding was applied during the study period.

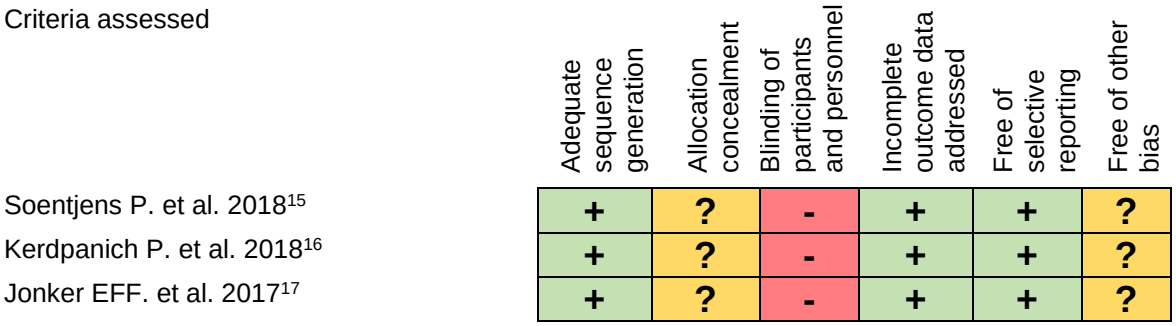

Figure 5: Assessment of risk of bias of RCT (Cochrane)

Assessment using Joanna Brigs Institute (JBI) for Non-RCT

The assessment is summarised in Figure 6 which showed that the study fulfilled the checklist criteria.

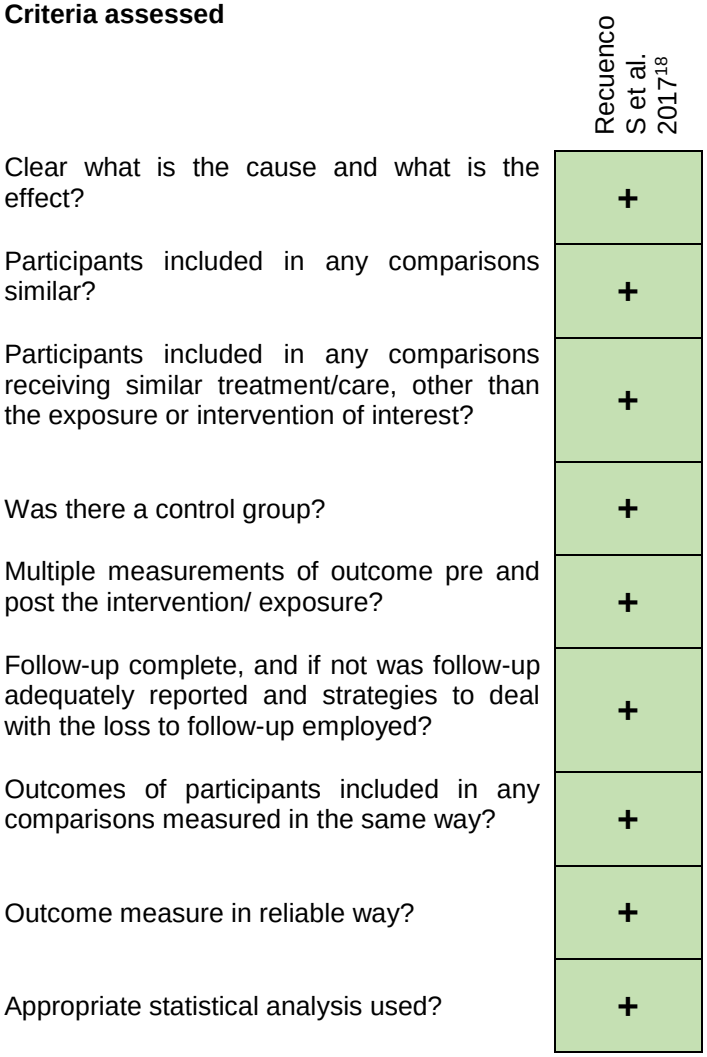

Figure 6: Assessment of risk of bias of quasi experimental studies non-RCT (JBI)

Assessment Using National Institute of Health (NIH) Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group

The risk of bias Pre-Post studies with no control group was assessed using NIH Quality Assessment Tool. The assessment is summarised in Figure 7. The study was having high risk of bias due to no blinding and the outcome measures were not statistically presented.

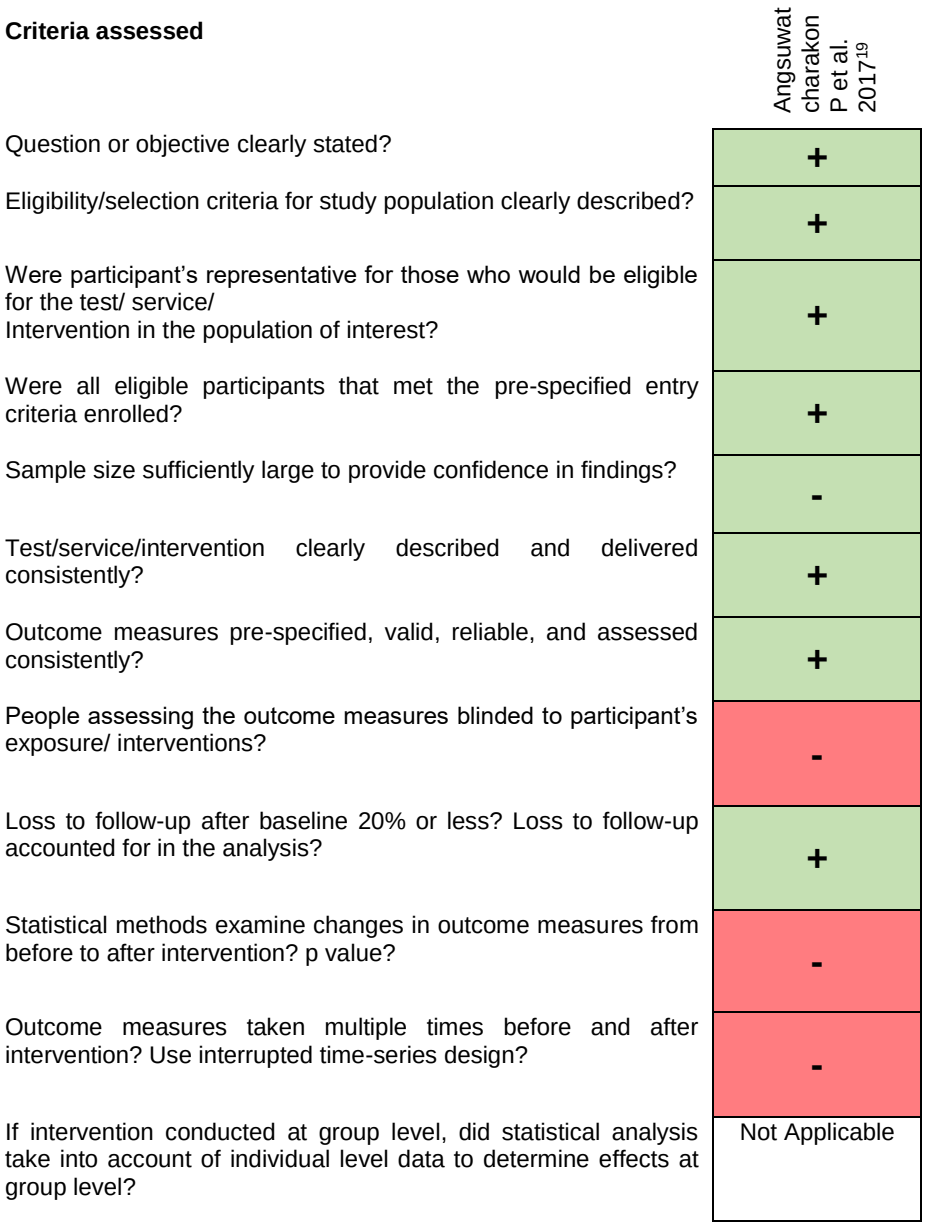

Figure 7: Assessment of risk of bias of pre-post studies with no control (NIH)

5.2. EFFICACY/ EFFECTIVENESS

The included studies consist of two studies on PEP and five studies on PrEP.

5.2.1 Comparison of Intradermal and Intramuscular Rabies Vaccine

Langedijk AC et al. (2018) conducted an SR and MA; the aim of the SR was to summarise the published data on the boost-stability of rabies immunization to date and the MA was to describe pre-booster seroconversion rates (SCRs) and pre- and post-booster geometric mean titres (GMTs) comparing IM and ID routes. The primary outcomes were the percentage of participants with antibody levels ≥ 0.5 IU/mL before booster vaccination on day 365 or later after primary immunization and the same percentage immediately after booster immunization. The secondary outcome measures were GMT and antibody range before and after booster at day 365 or later. In total, 36 studies (4,912 subjects who underwent rabies booster immunization more than one year after primary vaccination) were included. Those studies were published between 1984 and 2014. Of 36 studies included, 29 reported on short-term boost-stability and seven identified long-term boost-stability. The authors observed the outcomes mostly at day 7 and 14. The SR results of GMT and SCR for primary dose and booster dose for both routes are shown in table 2.[13, level1]

Table 2: SR results

	Primary vaccination	Booster vaccination
GMT	Higher after IM schedules than ID	GMTs >0.5 IU/mL in both routes after booster but higher in IM than ID
	Higher GMTs dropped <0.5IU/mL after ID administration compared to IM	
SCR	Not mentioned	100% in all studies

In MA, 19 studies on short-term boost-stability were included. Out of the 19 studies, 17 studies (1,504 subjects) were included for SCRs. The MA of SCRs showed that the pooled percentage for SCRs after ID immunization was 62% (95% CI 47,76, I^2 = 96.44%) which was significantly (p=0.005) lower than after IM immunization (90%; 95% CI 80,100, I^2=99.13%). Seroconversion rates after booster immunization, both ID and IM, were close to 100%, and therefore not eligible for MA. Meta-analysis on GMTs were also conducted, eight studies (1,660 subjects) were included for 'before booster immunization' and ten studies (1,955 subjects) were included for 'after booster immunization'. The results are summarized in table 3 where it shows that the lower limits of 95% CI for all routes after post-booster immunization were above 0.5 IU/mL. There was significant difference between ID and IM group for both pre-booster vaccination (p = 0.014) and post-booster vaccination (p = 0.003). The authors also reported that, one study which compared ID and IM, had follow up its cohort for five years after booster injection at year one. The study reported that SCR gradually decreased for both primary and booster doses over the five years to 80% (69/86 patients) in IM route and 54% (48/89 patients) in ID route.[13, level 1]

Table 3: MA Results

	Pre-Booster (Mean value; IU/mL)	Post-Booster (Mean value; IU/mL)
ID Group	0.49 IU/mL (95% CI 0.23,1.06) I^2 = 99.98%	17.64 IU/mL (95% CI 13.77,22.61) I^2 = 99.86%
IM Group	1.44 IU/mL (95% CI 0.91,2.25) I^2 = 99.98%	59.87 IU/mL (95% CI 64.64,104.39) I^2 = 99.86%
p-value	p-value = 0.014	p-value = 0.003

Preiss S. et al. (2018) conducted SR and MA to assess the immunogenicity, efficacy, and safety of a PCECV for PEP against rabies by IM or ID routes. Systematic search yield 48 studies which consisted of 33 interventions studies, 14 observational studies and one interventional and observational study. Most of the included studies estimate the outcomes for more than one subgroup, leading up to 55 estimates for immunogenicity, 10 estimates for efficacy and 48 estimates for safety. Meta-analysis for immunogenicity could not be performed because of missing data. In the SR of interventional studies using ID route, RVNA GMTs ≥0.5 IU/mL were reported on day 14 (D14) and day 90 (D90), regardless of the regimen used, with six studies reporting values ≥0.5 IU/mL up to day 365 (D365). Meanwhile the SR of all interventional studies used IM routes at various vaccination schedules reported the RVNA GMTs ≥0.5 IU/mL on D14, D90, and D365. Meta-analysis was conducted separately between ID and IM route as meta-analysis to compare the ID and IM routes of administration could not be performed because of the difference in duration of the measurements and difference in the populations studied. Fourteen interventional studies of ID route were included in the MA, the overall proportion of participants with adequate RVNA levels on D14 was 100% (95% CI: 99, 100%; I^2 = 0.0%; p = 0.91). Seventeen interventional studies of IM route were included in the meta-analysis, the overall estimate of the proportion of individuals with RVNA titres ≥0.5 IU/mL at D14, was 99% (95% CI: 97–100%; I^2 = 71.6%; p < 0.001). The authors also conducted subgroup analysis for each routes and the results at D14 are summarised in table 4.[14, level 1]

Table 4: Meta-analysis Results at Day 14

	Healthy Volunteers (RVNA ≥ 0.5IU/mL)	Bite Case (RVNA ≥ 0.5IU/mL)	People at Risk (RVNA ≥ 0.5IU/mL)
Intradermal (ID injection)	100% (95% CI 99, 100%) I^2 = 0.0%, p = 0.63	100% (95% CI 99, 100%) I^2 = 0.0%, p = 1.00	100% (95% CI 99, 100%) I^2 = 0.0%, p = 0.75
Intramuscular (IM injection)	99% (95% CI 95, 100%) I^2 = 71.6%, p < 0.001	99% (95% CI 95, 100%) I^2 = 35.4%, p < 0.19	96% (95% CI 95, 100%) I^2 = 73.9%, p < 0.001

Recuenco S et al. (2017) conducted single centre non randomised controlled trial to determine the immunogenicity of PCECV to induce adequate levels of RVNA GMT in subjects following schedule of three 0.1mL (0.25 IU/mL) ID doses as recommended by WHO compared to three (2.5 IU/mL IM) doses, or single booster doses. The study involved 128 healthy subjects age 20 to 60 years old. The participants were divided into naïve subjects (PrEP groups) or previously vaccinated group (Booster group). Those subjects were divided into four

subgroups; PrEP IM group, PrEP ID group, Booster IM group and Booster ID group. The PrEP group received three single dose of either 0.1mL of the rabies vaccine by the ID route, or 1.0mL by the IM route, given on day 0, day 7 and day 21. For persons in Booster group, one dose of vaccine was administered either ID (0.1mL) or IM (1.0mL) on day 0 only. The IM route was used as a comparison control. The primary outcome was the proportion of subjects who developed RVNA GMT of at least 1:5 (~0.1 IU/mL) or highest against rabies virus, 14 days after completion of the vaccination schedule. The secondary outcome was serum virus neutralising antibody (VNA) titers measured two, four and five months after the receipt of full vaccination schedule. All participants in the four groups achieved the GMT level of ≥1:5;~ 0.1 IU/mL 14 days after completion of their correspondent PrEP or booster vaccination regimen, indicating optimal seroconversion. The VNA antibody levels ≥1:5 were observed in PrEP group before the time of 3rd dose of vaccine on day 21. Then the GMT values for each PrEP group peaked at 14 days after the 3rd dose of vaccine and decrease slowly until at the end of the follow-up (160 days after vaccination completed) but all the values maintained over 0.5 IU/mL. However, the PrEP values for IM group was approximately two fold of the ID group and the difference were statistically significant at all the visit except for base line; baseline ($p = 0.408$), day 7 ($p = 0.001$) and day 21 ($p = 0.002$). For booster, peak VNA GMTs were observed at day 14 for both booster groups. Rapid increase in VNA for both ID and IM booster group from day 0 to day 14 showed only a gradual decline over the 160 days of follow up. At day 160, the VNA GMTs were~ 5-fold higher than the starting levels in those receiving the ID revaccination and approximately 10-fold higher than starting levels in those receiving IM. However, the GMT levels for the Booster IM group were between 2- and 3-fold higher than the GMT values for the Booster ID group which was statistically significant ($p=0.009$).[18, level II-1]

Jonker EFF et al. (2017) conducted a non-blinded randomised control trial (RCT) to determine the optimal PrEP vaccination regimen either ID or IM route that would require only a single visit to the clinic in order to produce adequate memory response in all subjects after one year. The study was held in Travel Clinic of Leiden University Medical Centre, Netherlands. The subjects were 30 healthy volunteers between age of 18 and 31 years' old who had no history of any previous rabies vaccination. Those subjects were randomly assigned to four groups of four regimens for primary rabies vaccination using computer-generated permuted block randomisation. The groups are shown in table 5. All 30 subjects completed the study. One month after primary vaccination, there was overall 28 subjects or 93% (95% CI 85,100%) seroconversion rate for one-visit priming schedules. One year after primary vaccination, only eight out of 30 subjects still had RVNA GMT > 0.5 IU/mL; Group A (three subjects), Group B (two subjects), Group C (one subjects) and Group D (two subjects). Then one week after first booster dose (one year after primary vaccination), 30 subjects seroconverted within one week of the first booster dose even in those who did not seroconvert after primary vaccination. Revaccination were started and at day 7, the GMT level increased 251-fold in Group A and 48-fold to 86-fold in the ID groups; the difference in fold increase was significant ($p < 0.03$) for Group A compared to Group C and D. The authors also looked at dose-response relationship, although Group A showed the highest GMT post-booster, no dose-response relationship was found in the study when all groups were compared. Besides, serology performed at day 3 post-booster did not show a difference in GMT from the pre-

booster baseline. On the other hand, reverse cumulative distribution curve of RVNA GMTs at day 7 post-booster showed the highest titers in Group A; $p < 0.015$ for each ID group versus IM. The authors concluded that effective rabies PrEP for travellers may be achieved in a single visit with 100% booster response after one year even in those who do not seroconvert after the priming dose.[17, level II-1]

Table 5: Group Characteristics

Group	Regimen	No. of Patients (N = 30)
Group A	1-site 0.5ml IM (standard dose)	10
Group B	1-site 0.1 ml ID (equivalent to 20% of standard dose)	10
Group C	2-site 0.1 ml ID (40% of standard dose)	5
Group D	3-site 0.1ml ID (60% of standard dose)	5

5.2.2 Intradermal Rabies Vaccine at Different Schedule / Regimen

Soentjens P. et al. (2018) conducted single centre, randomised, open label clinical trial to compare an immunogenicity seven days after a single ID booster injection following two different priming schedules one to three years earlier: a double-dose two-visit (2ID) rabies ID vaccination schedule versus a single-dose three-visit schedule (3ID). The study involved 498 healthy participants who were recruited from the Belgian Armed Forces and had no previous history of rabies vaccination. Those subjects were randomised into two groups: intervention group; 2ID group (249 subjects) and control group; 3ID group (249 subjects). The 2ID group involved two intradermal injections with dose of 0.1 mL in 2 separate injection sites on day 0, and two injections in separate sites on day 7. The main outcome was observed adequate rabies antibody titres >0.5 IU/mL seven days following booster injection administered one to three years after primary vaccination. Meanwhile, the 3ID group involved one intradermal injection with dose of 0.1 mL on days 0, 7, and day 28. In 2ID group, 242 patients completed 2ID schedules. Out of 242, 211 (87%) subjects received booster and from 211 subjects, 183 (75%) were included in per-protocol analysis. In 3ID group, 240 subjects completed 3ID schedules. Out of 240, 200 subjects (83%) received booster and from that 185 subjects (77%) were included in pre-protocol analysis. The intention to treat (ITT) analysis, for adequate rabies antibody titres at day 7 after single booster for both group with one to three years are summarized in table 6. In the per-protocol analysis, all subjects in both groups displayed rabies antibody titres >0.5 IU/mL on day 7 following a single 0.1ID booster dose. The authors also assessed the level of rabies antibody titres >10 IU/mL following a single 0.1ID booster dose. The proportion of participants reaching rabies antibody titres level >10 IU/mL level in the 2ID group was higher than in the 3ID group [96% versus 83% with a difference of 13% (95% CI 7, 19)]. Then following the booster vaccination offered one to three years later, subjects in the 2ID group exhibited a GMT of 37 IU/mL (95% CI 33, 42), compared to a GMT of 25 IU/mL (95% CI 22, 29) for the 3ID group ($p<0.001$). Other outcome was GMT of rabies antibody; the GMT values on the day of booster injection in the 2ID schedule were higher (3.4 IU/mL, 95% CI 2.9, 3.9) compared to the 3ID schedule (2.0 IU/mL, 95% CI 1.7, 2.4) ($p<0.001$). Post-booster GMT levels were also higher in

favour of the 2ID schedule when analysed by booster dose timing, these were only significant when the interval between PrEP and PEP was greater than 25 months (p= 0.0002).[15, level 1]

Table 6: Number of Subject Reached >5 IU/mL at Day 7 After Primary Vaccination (ITT Analysis)

	1st year	2nd year	3rd year
2ID Group (n = 211)	59%	35%	6%
3ID Group (n = 200)	54%	38%	8%

Kerdpanich P. et al. (2018) conducted phase III multicentre randomised controlled trial in four centres in Philippines and two centres in Thailand. The purpose of the study was to assess non-inferiority of the immune response of the 4-site/1-week ID PEP regimen to that of the currently recommended 2-site/Thai Red Cross (TRC) ID regimen of rabies vaccine with or without human rabies immunoglobulin (HRIG) administration which was measured by the percentage of participants with RVNA concentrations ≥0.5 IU/mL in the whole study population at day 49. The non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI around the difference [(Group A1 + Group A2) – (Group B1 + Group B2)] in the percentage of participants with RVNA concentrations -0.5 IU/mL was greater than -5% (> 0.667). Another objective was to compare antibody responses at day 7, day 14, day 90, day 180 and day 365 in terms of RVNA GMCs and percentage of participants with RVNA concentrations ≥0.5 IU/mL following each rabies vaccine. The rabies vaccine used was PCECV which each injection requires 0.1mL of vaccine. The subjects were 885 healthy individuals with no history of rabies vaccination and no previous exposure to rabies. They were divided into four groups which was based on age strata and randomly assigned into two regimens group (group 4 site/1-week regimen and group 2-site/TRC regimen). The subjects below 18 years old were randomly assigned at 1:1 ratio at group A1 or B1 and subjects more than 18 years old were randomly assigned at ratio of 2:1:2:1 into four regimens group A1, A2, B1, and B2. The groups description is shown in table 7. Out of 885 subjects, 875 subjects completed the study. At day 49, the percentages of participants with RVNA level ≥ 0.5 IU/ml were 99% (95% CI 98%,100%) in ID regimen 4-site/1-weekand and 100% (95% CI 99%, 100%) in ID regimen 2-site/TRC. The lower limit of the 2-sided 95% CI on the between-group difference was -2.4% which was above the pre-specified non-inferiority margin. The whole population of participants in both regimens achieved GMT ≥ 0.5 IU/ml by day 14 and 90% in 4-site/1-week regimen and 83% in 2-site/TRC regimen maintained adequate GMC concentrations at day 365 after first vaccination. The RVNA GMCs peaked at day 14 and declined at subsequent time points. At day 49, the RVNA GMC ratio was 0.46 (95% CI 0.37, 0.58) and the lower limit of the 95% CI was below the pre-specified non-inferiority margin. However, at day 365, higher immune response was observed in the groups which received the 4-site/1-week regimen than in those receiving the 2-site/TRC regimen. The assessment based on the administration of HRIG are shown in table 7.[16, level 1]

Table 7: Group Description and HRIG Assessment

Groups	Age Groups	HRIG* Assessment (Group A1 vs Group B1) (Group A2 vs Group B2)
Group A1 *(4-site/1-week ID regimen alone)*	Age <18 years Adults ≥18 years	Day 14: adequate RVNA levels 95% maintained adequate neutralising levels for 1 year following 1st vaccination
Group A2 *(4-site/1-week ID regimen with concomitant HRIG administration at 1st visit)*	Adults ≥18 years	Comparable RVNA ≥0.5 IU/mL with B2 of all time points except day 90 Day 90: adequate RVNA levels was significantly lower in Group A2 than in Group B2
Group B1 *(2-site/TRC* ID regimen alone)*	Age <18 years Adults ≥18 years	Day 14: adequate RVNA levels 87% maintained adequate neutralising levels for 1 year following 1st vaccination
Group B2 *(2-site/TRC Id regimen with concomitant HRIG administration at 1st visit)*	Adults ≥18 years	Comparable RVNA ≥0.5 IU/mL with B2 of all time points except day 90 Day 90: adequate RVNA levels was significantly lower in Group A2 than in Group B2

*HRIG: human rabies immunoglobulin; TRC: Thailand Red Cross; ID: Intradermal

Angsuwatcharakon P. et al. (2017) conducted pre- and post-intervention study to assess the immunogenicity of chromatographically purified Vero cells rabies vaccine (CPRC) when administered ID for PEP in paediatric patients. The study involved 39 of non-immunized patients aged less than 15 years' old who actually had possible rabies exposure and classified as WHO categories II or III. Those patients were recruited at outpatient rabies immunization clinic of Thai Red Cross Society. The ID rabies vaccine schedule was 2-site ID Thai Red Cross Regimen (TRC-ID; 2-2-2-0-2-0) using two 0.1mL ID doses of CPRV with or without RIG for children in Thailand. The results recorded that 25 patients (64.1%) with severe bite wounds (rabies exposure WHO category III) received rabies immunoglobulin [(11 cases received equine rabies immunoglobulin and 14 cases received human rabies immunoglobulin (due to positive skin test or were younger)) concomitant with rabies vaccine on day 0]. Prior to rabies vaccination (day 0), all paediatrics patients showed undetectable Nab titers. All the patient had reached an adequate immune response for rabies (Nab titers above 0.5 IU/mL) either with or without RIG on day 14 and 90 day as showed in table 8.[19, level II-2]

Table 8: Immune Response of ID Rabies Vaccine

Day	With RIG	Without RIG
Day 14	16.17 IU/mL (range 4.00 - 65.40 IU/mL)	14.14 IU/mL (range 2.23 - 39.74 IU/mL)
Day 90	4.37 IU/mL (range 0.77-14.67 IU/mL)	9.48 IU/mL (range 2.18-23.60 IU/mL)

5.3 SAFETY

United State of Food and Drug Administration (USFDA) approved the use rabies vaccine for IM route only. At the moment the use of rabies vaccine via ID in US remained off-label. However, the WHO has recommended the used of ID rabies immunization as an alternative to IM immunization.[20]

5.3.1 Comparison of Intradermal and Intramuscular Rabies Vaccine

Preiss S et al. in their study found that in 16 interventional studies which reported ID administration of PCECV, the most frequently reported local adverse events (AES) were erythema, itching, induration, lymphadenopathy, and pain, while the most common systemic AEs reported were headache and fever or having a feverish feeling. Meanwhile for IM route, 15 interventional studies reported the most frequent locals AEs in IM route were itching, erythema and pain and for the most common reported systemic AEs were myalgia, headache, fever or feverish feeling. Comparing ID route and IM route AEs; erythema, induration, and lymphadenopathy were more frequently reported for ID compared with IM-route. In a study conducted among healthy hospital staff, veterinary students, and patients with possible risk of infection, pain was more frequently reported in the IM group than in the ID group ($p< 0.001$); however, ID caused more local irritation, erythema, and induration (92%) compared with IM vaccination (66%) ($p < 0.02$).[14, level 1]

Recuenco S et al. reported no serious AEs during the study. Most reported AEs were local and mild AEs. The most frequent local complained were erythema (61%), induration (40%) and tenderness (36%) at injection site. On the other

hand, the most frequent systemic AEs were headache (19%), fatigue (18%), fever (11%) and insomnia (8%). Erythema (80%) and induration (58%) were the most frequent complaints among ID groups which was lower in IM groups (erythema 15% and induration 8%). At 14 days after vaccination, all participants in the PrEP ID group had at least one AE compared to only 67% of the participants in the PrEP IM. Meanwhile, in the booster group, participants in ID arm presented more AEs (20/31) than in IM arm (8/33) whereby erythema was the main complaint in ID arm and almost none in IM arm.[18, level II-1]

Jonker EFF et al. reported no serious AEs during the study period. The AEs occurred after both primary and booster vaccination. After the primary vaccination, eight out of 30 subjects reported localized erythema which appeared only in the ID groups (36.67%), myalgia (26.67%) and fatigue (19.35%). Meanwhile, after booster vaccination, myalgia occurred in 26.67% subjects with one of them reporting swollen axillary lymph nodes and another one reporting fatigue.[17, level II-1]

5.3.2 Intradermal Rabies Vaccine at Different Schedule / Regimen

Soentjens P et al. also assessed the safety issue in their RCT. They found that serious AEs included reversible diplopia and hemianopsia that occurred during the primary vaccination session 14 days after receiving the final rabies vaccine injection (3ID schedule) and some days after receiving a measles-rubella-mumps vaccine in another medical centre, in violation to the protocol. Also one case of oesophagitis and one case of oesophagitis with dyspnea, angioedema and urticarial which occurred following a booster dose (2ID schedule). Non-serious AEs, were local irritation at the injection site (mild and transient) following primary vaccination which occurred more frequently in the 3ID compared to the 2ID schedule (51.8% versus 43.4%, p=0.07). In contrast local irritation was more often observed following the booster dose in the 2ID group (38.8% vs 48.8%, p=0.03). The number of subjects with systemic discomfort related to injections was very low and did not differ significantly between the two groups (3ID versus 2ID) following primary vaccination (14.5% vs 11.6%, p=0.42, respectively) or booster injection (5.4% vs 5.8%, p=1, respectively.[15, level 1]

Kerdpanich P et al. observed solicited and unsolicited AEs between 4-site/1-week regimen groups (GA1 and GA2) and 2-site/TRC regimen groups (GB1 and GB2).[14] Solicited is a method of collecting AEs in-spontaneously and unsolicited is a method of collecting AEs spontaneously.[19] At least one solicited AEs was reported in the groups (57% in GA1 and 65% in GA2) and at least one unsolicited AEs was reported in the groups (59% in GB1 and 62% in GB2). The solicited and unsolicited AEs is each groups are shown in table 9.[16, level 1]

Table 9: Solicited and Unsolicited Adverse Events

AEs	Local Reactions	Systemic Reactions	Severe	Serious Reactions
Solicited AEs	More frequent in the 1±5 years' age stratum [Groups A1 (76%) and Group B1 (68%)] of children than in the other age strata (31%±41% of individuals receiving the 4-site/1-week ID regimen and 33%± 41% of individuals receiving the 2-site/TRC ID regimen) • Tenderness in the 1±5 years' age stratum (ranging from 7% to 21% of children across study groups • Injection site pain in the 6±17 years' age stratum (in 4±14% of participants in all groups), and • Injection site erythema in the ≥18 years' age stratum (ranging from 1% to 16% of adults across study groups).	Reported in 33%±42% of participants receiving the 4-site/ 1-week ID regimen and 33%±46% of participants receiving the 2-site/TRC ID regimen and were more frequently reported in the ≥18 year of age stratum ➢ Most frequent solicited systemic AEs in the 1±5 year of age stratum were: • Fever (reported in 7% of children in Group A1 and 17% in Group B1) and • Sleepiness (14% in children Groups A1 and B113% of children in group B1 ➢ Most frequent solicited systemic AEs in 6±17 year of age stratum were: • Headache (in 13% of participants in Group A1 and 16% in Group B1) and • Fatigue (for 12% of participants in Group A1 and 11% in Group B1 ➢ Most frequent solicited systemic AEs in participants aged ≥18 years were: • Headache (ranging from 19% in Group B1 to 35% in Group B2)	Severe solicited local and systemic AEs were reported in 0%±2% of participants in all age groups; most solicited AEs were mild to moderate in intensity.	Serious adverse events (SAEs) were reported in 3%±6% of participants; none of them were considered related to vaccination. All SAEs except 1 (HIV infection in an adult in Group A1) were recovered/ resolved by the end of the study No deaths were reported during the study

AEs	Local Reactions	Systemic Reactions	Severe	Serious Reactions
		• Fatigue (ranging from 19% in Group A2 to 27% in Group B2		
Unsolicited AEs	Unsolicited AEs were reported in • Group A1: 73% and • Group A2: 84%, • Group B1: 79% and • Group B2: 82% Unsolicited AEs possibly or probably related to vaccination were reported in • Group A1: 66% • Group A2: 84% • Group B1: 65% and • Group B2: 80% Most frequently reported AEs after any vaccination were in the "general disorders" and "administration site conditions" "system organ class", followed by "infections and infestations" Overall, the most frequent AE was injection site erythema, with incidences ranging from 37% (Group B1) to 61% (Group A2) of participants in all groups No AEs leading to withdrawal from the study were reported.		Incidence of severe unsolicited AEs at least possibly or probably related to vaccination was • Group A1: 1% • Group B1: 1% • Group A2: 0% • Group B2: 0%	

Angsuwatcharakon P et al. reported that most of their subjects experienced local adverse reactions at site of ID injection, such as local erythema (66.75), induration (46.8%), pain (25.0%) and itching (26.9%) and these AEs were self-limiting within two days and required no treatment. Myalgia and fevers was reported in 12.8% and 5.1% of patients, respectively after vaccination. At one year after vaccination, adequate follow-up was achieved in 76.9% of the cases and all patients were alive and healthy. No serious AEs were observed after vaccination.[19, level II-2]

5.4 COST/COST-EFFECTIVENESS

In Ministry of Health, the price of Rabies Vaccine (Inactivated) Injection per vial (Verorab): ~RM480 (2015).[21] There was no local economic evaluation retrieved. No evidence on cost-effectiveness retrieved.

5.5 ORGANIZATIONAL

Currently MOH is following Interim Guideline for Human Rabies Prevention & Control in Malaysia. Guideline is divided into three main topics which are 1) Surveillance of human rabies 2) Medical response for human rabies/human exposes to rabid animals and 3) Laboratory criteria for diagnosis of human rabies.[6] Since human rabies incidence is high in Sarawak, the Sarawak Plan of

Action for Rabies Elimination by 2020 was prepared with lists of strategies including animal vaccination strategy as well as human vaccination schedule.[22]

Another issue is on the ID injection route. The ID injection is an injection administered into the dermis, just below the epidermis. The techniques require skills and it has the longest absorption time of all parenteral routes. Once the ID injection is completed, a bleb (small blister) should appear under the skin.[22] If the bleb does not appear during the injection, the particular dose must be repeated.

5.6 LIMITATIONS

This technology review has several limitations. Although there was no restriction in language during the search, but only English full text articles were included in this report. The studies included in this review have several limitations including small sample size.

6. CONCLUSION

There were fair to good level of evidence retrieved on ID rabies vaccine. Out of seven included studies in this technology review, two SR and MA, 1 non RCT and 1 non-blinded RCT compared ID routes and IM routes of rabies vaccine. Whereas other studies (two RCTs and 1 pre- and post-intervention study) compared different regimes and schedule of intradermal rabies vaccine. Two studies were on PEP and the other five studies were on PrEP.

Efficacy / Effectiveness

Pre-Exposure Prophylaxis (PrEP)
Comparing PrEP by ID route and IM route, both routes achieved seroconversion and the RVNA GMTs were above the desire level. However, the RVNA GMTs in IM route was significantly higher than ID route. After booster dose, both routes showed rapid increase in virus neutralizing antibody GMTs (above the desired level). However, the GMTs level in IM route was significantly higher than in ID route.

One study showed that high seroconversion rate after one month of single visit of PrEP rabies vaccination with ID route. However, after one year the RVNA GMTs declined and was later increased with first booster dose. The seroconversion was also completed within one week of the first booster dose. The seroconversion rate and the RVNA GMTs was higher in IM route compared to the ID route.

For PrEP with ID rabies vaccine at different schedule and regimes, more patients with 2ID regime achieved GMT level ≥ 0.5 IU/ml and ≥ 10 IU/ml after one- or three-years primary vaccination schedules compared to 3ID regimes. On the other hand, one study reported that 4-site/1-week schedule and standard regimen of TRC (2-site/TRC) schedule achieved the same adequate RVNA GMT level of ≥ 0.5 IU/ml. However, the immune response at day 365 was higher in 4-site/1-week regimen than 2-site/TRC regimen.

As for the RIG administration, when comparing 2-site ID TRC regimen with or without RIG, both regimes reached adequate immune response in WHO categories II and III paediatric patients on day 14 and day 90.

Post Exposure Prophylaxis (PEP) Rabies Vaccination
After primary and booster vaccination of PEP, both routes either IM or ID achieved seroconversion rates and the RVNA GMT level of ≥0.5 IU/ml. Both levels were higher in IM route compared to ID route.

Safety

Currently, no rabies vaccine via ID route is approve by USFDA and the use of ID rabies vaccine in US remained off-label.

The most common AEs of rabies vaccine when comparing ID route and IM route can be divided into local AEs and systemic AEs. Compared with IM route, erythema, induration and lymphadenopathy were reported more frequently in ID route.

When comparing 3-ID schedule and 2-ID schedule, serious AEs which included reversible diplopia and hemianopsia occurred during final dose of primary vaccination of 3-ID schedule while oesophagitis with dyspnea, angioedema and urticarial occurred during booster dose of 2-ID schedule. For non-serious AEs, local irritation at the injection site during primary vaccination occurred more frequently in 3-ID schedule compared to 2ID schedule. However, during booster local irritation occurred more often in 2-ID schedule. Systemic AEs was very low in both schedule and not significant.

Referring to pre- and post-intervention study of ID rabies vaccine in paediatrics patients, more local irritations at ID injection sites such as local erythema, induration, pain and itching which were self-limiting within two days and no treatment were required. Others AEs were myalgia and fevers.

Cost/Cost-Effectiveness Analysis
No cost-effectiveness analysis retrieved
No local cost analysis was retrieved.

Organizational

Ministry of Health Malaysia has come out with Interim Guideline for Human Rabies Prevention and Control in Malaysia while Sarawak state had developed Sarawak Plan of Action for Rabies Elimination by 2020.

The ID route techniques requires skills and if the bleb does not appear during the injection, the particular dose of the rabies vaccine must be repeated.

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Part B

BACKGROUND

Rabies is a highly fatal zoonotic disease caused by Lyssavirus.[1] This disease now kills more than 69,000 people every year mostly in Asia and Africa. In 1999, the World Association (WHO) for Animal Health to declare Malaysia rabies free in 2012 and since then there was no major outbreak until the recent outbreak (July 2015 in Perlis).[2]

According to WHO, an estimated 35,172 human deaths (59.6% of global deaths) and loss of approximately 2.2 million disability-adjusted life years (DALYs) occur per year in Asia due to dog-mediated rabies where India accounts for the most deaths in Asia (59.9% of human rabies deaths) and globally (35% of human rabies deaths). The cost of PEP is highest in Asia, with estimates up to US$ 1.5 billion per year. The overall economic cost of dog-mediated rabies was estimated in a probability decision-tree model to be US$ 8.6 billion (95% CI: 2.9, 21.5 billion).[3]

Rabies vaccination program is an important element in preventing rabies either in humans or animals. The WHO recommend two main immunizations strategies for human which are pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) for the prevention of human rabies.[1,4] According to Interim Guideline for Human Rabies Prevention & Control in Malaysia by the Disease Control Division, Ministry of Health (MOH), general guideline for dog bite management according to category of exposure that determines the indicated PEP procedure is as follows:[5]

a. Category I: Touching or feeding an animal or licks on intact skin: no exposure; PEP not indicated;
b. Category II: Nibbling of uncovered skin, minor scratches or abrasions without bleeding: exposure; PEP indicated with vaccine; to be treated as category III if exposure was to a bat; and
c. Category III: Single or multiple transdermal bites or scratches, contamination of mucous membranes with saliva from licks, licks on broken skin, exposure due to direct contact with bats: severe exposure

The vaccine is administered via intramuscular (IM) only.[5] However, based on recent report from the WHO, administration of rabies vaccine with intradermal (ID) route for either PEP or PrEP, have efficacy equivalent to or higher than the same vaccine administered by IM route.[1]

For the ID route, one dose is 0.1 mL of rabies vaccine (irrespective of the vaccine brand). The vaccine in one vial can therefore be fractionated to provide five to ten doses for ID administration, depending on the vial size (0.5 mL or 1.0 mL).[1] In 1992, WHO approved it for use in developing countries which face a shortage of rabies vaccine due to paucity of funds. For the IM route one dose is one vial of vaccine per patient.[6] However, the current route of administration in the rabies vaccine leaflet is IM not ID, hence it has been used off-label. Compared to IM recommended schedule, the ID schedules offer advantages through savings in costs, doses and time.[1] Head of Zoonosis Sector of Disease Control Division requested further assessment on ID rabies vaccine injection given as PrEP and PEP.

OBJECTIVES / AIM

To compare the cost of IM and ID post-exposure and pre-exposure rabies vaccine treatment

METHODS

Cost-minimization analysis (CMA) was conducted from the healthcare system perspective. The CMA of comparing an intradermal route of rabies vaccine against intramuscular route was performed. The model was a direct calculation which was developed based on available local data and was created in a spreadsheet (Excel 2010, Microsoft Corporation). The model provides the Disease Control Division an opportunity to include their own direct costs and reimbursements amounts from any specific payer to arrive at real-time values.

MODEL INPUTS:

Clinical Effectiveness

The efficacy/effectiveness of ID route rabies vaccine was retrieved from published journal as well as based on WHO requirement. The WHO reported that vaccine potency showed that current vaccines (≥2.5 IU/IM dose), when administered by intradermal (ID) route for either PEP or PrEP, have efficacy equivalent to or higher than the same vaccine administered by IM route.[1]

Resources and Cost Data

Cost data (Table 1-3) was collected from local data as well as published literature.

i) Bite cases and Vaccinated Subjects (2017 to February 2019)

Table 1: Number of bite cases and vaccinated subjects of PEP

Year	Region	Bite Cases	Vaccinated (PEP)	Routes of Administration	Sources
2017	Sarawak	7,810	2,298	IM only	Disease Control Division
	Perak	2	2	IM only	Disease Control Division
2018	Sarawak	16,420	5,210	IM & ID	Disease Control Division
	Perak	0	0	IM only	Disease Control Division
2019 (January-February)	Sarawak	1,813	359	IM & ID	Disease Control Division
	Perak	134	54	IM only	Disease Control Division

Table2: Number of subjects underwent PrEP

Year	Region	Pre-Exposure Prophylaxis	Vaccinated	Routes of Administration	Sources
2018	Sarawak	250	250	IM only	Disease Control Division
2019	(Plan)	300		IM / ID	Disease Control Division

ii) Cost and Dose of Rabies Vaccine

All prices are given in Ringgit Malaysia and were based on current currency rate, except for out-patient cost which was adjusted to 2018 using Malaysia Consumer Price Index (CPI). The price for rabies vaccine per vial was directly quoted from Disease Control Division based on their current (2018) purchasing price.

Table 3: Data of Cost and Dosage

Parameter	Price/Dosage	Sources
Rabies vaccine/vial (0.5ml/vial) (RM)	[redacted]	Disease Control Division
Out-Patient Cost (RM)	RM153.71	Loganathan T et al 2016[7] & https://data.worldbank.org[8]
Syringe 1ml (RM)	[redacted]	Pharmacy Store, HTAA, Kuantan

Table 4: Regimen of Rabies Vaccine in Malaysia Practice

Parameter	Dose	Visit/Number of dose)	Sources
PEP IM dose/person (ml)	0.5 ml (1-site/person)	Day 0, 3, 7 and 14 @ 28 (1-1-1-1)	Disease Control Division & Summary of 2017 Updates, WHO[9]
PEP ID dose/person (ml)	0.1 ml (2-site/person; 0.1ml each site)	Day 0, 3, and 7 (2-2-2)	Disease Control Division & Summary of 2017 Updates, WHO[9]
PrEP IM dose/person (ml)	0.5 ml (1-site/person)	Day 0 and 7 (1-1)	Disease Control Division & Summary of 2017 Updates, WHO[9]
PrEP ID dose/person (ml)	0.2 ml (2-site/person; 0.1ml each site)	Day 0 and 7 (2-2)	Disease Control Division & Summary of 2017 Updates, WHO[9]

Limitations

1) Wastage for the rabies vaccine has been considered in all scenarios given, where each patient used at least one vial of rabies vaccine at a time. Any excess will be discarded after 6-8 hours.
2) The total cost of rabies vaccination was calculated based on per visit and not per dose received at a particular time.
3) Since ID rabies injection data from Sarawak was not separated from IM, the Disease Control Division suggested that number of ID route administration was half from the number of total vaccinated subjects in year 2018 and 2019.

RESULTS

Scenario 1 (Table 5.1-5.3) was referred to the current practices based on primary data provided by Disease Control Division from year 2017 up to February 2019 which is considered as the base-case. The data were obtained from two outbreak regions; Sarawak and Perak. For Sarawak, the vaccinated data was available for both routes IM and ID, however, ID route was only started from April 2018 just after they received special approval from Director General of Health specifically for Sarawak only. Scenario 2 to Scenario 5 referred to several situations which probably might applied during

practice. Scenario 2 (Table 6.1-6.3) is a scenario where 50% of vaccinated persons will receive IM and another 50% will received ID route of rabies vaccine. Scenario 3 (Table 7.1-7.3) is a scenario where all vaccinated persons receive ID route Rabies vaccine and all vaccinated persons in Scenario 4 (Table 8.1-8.3) receive IM route of Rabies vaccine. Scenario 5 (Table 9.1-9.3) is a scenario where the used of rabies vaccine per vial will be optimised; one vial of rabies vaccine 0.5ml/vial is maximised for 2 persons. The analyses will discuss further based on the total cost of vaccination per year which already included cost in Sarawak and Perak region.

Comparison between first two scenarios; total cost for one year of rabies vaccination procedures was decrease about 4.07% in Scenario 2 than Scenario 1. The cost saving is more in Scenario 2 if compared with Scenario 4 where all persons will be vaccinated using IM route; 14.29%.

Then, comparing the total cost per year between ID route (Scenario 3) and IM route (Scenario 4), the total cost saving is 25% more in Scenario 3. Another scenario to be highlighted was the optimum used of vaccine rabies per vial which was 2 persons per vial per visit (Scenario 5). Comparing Scenario 4 to Scenario 5, the cost per person was more cost saving in Scenario 5 (38.83%). The analysis for such scenarios differences are shown in table 11.

Scenario Analysis

1) Scenario 1: Current Practice (**Base-Case**)

Table 5.1: Current PEP Practice in Sarawak Region

Year	Route of Administration	Bite Cases	Total Vaccinated	Vaccinated (by Route)	Cost/Person (Full dose/visit)	Total Cost in 3 Years
2017	Intramuscular	7,810	2,298	2,298	RM976.16	RM2,243,215.68
	Intradermal	0	0	0	0	0
2018	Intramuscular	16,420	5,210	2605	RM976.16	RM2,542,896.80
	Intradermal			2605	RM732.12	RM1,907,172.60
2019 (Jan-Feb)	Intramuscular	1,813	359	180	RM976.16	RM175,220.72
	Intradermal			180	RM732.12	RM131,415.54
Total in 3 Years		**26,043**	**7,867**			**RM6,999,921.34**
Average Total in 1 Year		**8,681**	**2,622**			**RM2,333,307.11**

Table 5.2: Current PEP Practice in Perak Region

Year	Route of Administration	Bite Cases	Vaccinated	Cost/Person	Total Cost in 3 Years
2017	Intramuscular	2	2	RM976.16	RM1,952.32
2018	Intramuscular	0	0	0	RM0.00
2019 (Jan-Feb)	Intramuscular	132	52	RM976.16	RM50,760.32
Total in 3 Years		**134**	**54**		**RM52,712.64**
Average Total in 1 Year		**45**	**18**		**RM17,570.88**

Table 5.3: Current PrEP Practice Among DVS and PBT

Year	Route of Administration	Pre-Exposure Subjects	Vaccinated	Cost/Person	Total Cost in 3 Years
2018	Intramuscular	250	250	RM488.08	**RM122,020.00**
2019 (Plan)	Intramuscular	359	359	RM488.08	**RM175,220.72**

2) Scenario 2: All subjects received either ID route or IM route Rabies Vaccine for PEP or PrEP

Table 6.1: Current PEP Practice in Sarawak Region

Year	Route of Administration	Bite Cases	Total Vaccinated	Vaccinated (by Route)	Cost/Person (Full dose/visit)	Total Cost in 3 Years
2017	Intramuscular	7,810	2,298	1,149	RM976.16	RM1,121,607.84
	Intradermal			1,149	732.12	RM841,205.88
2018	Intramuscular	16,420	5,210	2605	RM976.16	RM2,542,896.80
	Intradermal			2605	RM732.12	RM1,907,172.60
2019 (Jan-Feb)	Intramuscular	1,813	359	180	RM976.16	RM175,220.72
	Intradermal			180	RM732.12	RM131,415.54
Total in 3 Years		**24,043**	**7,867**			**RM6,719,519.38**
Average Total in 1 Year		**8,014**	**2,622**			**RM2,239,839.79**

Table 6.2: Current PEP Practice in Perak Region

Year	Route of Administration	Bite Cases	Vaccinated (by Route)	Cost/Person	Total Cost in 3 Years
2017	Intramuscular	2	1	RM976.16	RM976.16
	Intradermal		1	RM732.12	RM732.12
2018	Intramuscular	0	0	0	0
	Intradermal		0	0	0
2019 (Jan-Feb)	Intramuscular	132	26	RM976.16	RM25,380.16
	Intradermal		26	RM732.12	RM19,035.12
Total in 3 Years		**134**	**54**		**RM46,123.56**
Average Total in 1 Year		**45**	**18**		**RM15,374.52**

Table 6.3: Current PrEP Practice Among DVS and PBT

Year	Route of Administration	Pre-Exposure Subjects	Vaccinated	Cost/Person	Total Cost in 3 Years
2018	Intramuscular	250	125	RM488.08	**RM61,010.00**
	Intradermal		125	RM488.08	**RM61,010.00**
2019 (Plan)	Intramuscular	359	180	RM488.08	**RM87,854.40**
	Intradermal		180	RM488.08	**RM87,854.40**

3) Scenario 3: All subjects received ID route Rabies Vaccine either for PEP or PrEP

Table 7.1: All subjects Received ID route Rabies Vaccine for PEP in Sarawak Region

Year	Route of Administration	Bite Cases	Vaccinated	Cost/Person	Total Cost in 3 Years
2017	Intradermal	7,810	2,298	RM732.12	RM1,682,411.76
2018	Intradermal	16,420	5,210	RM732.12	RM3,814,345.20
2019 (Jan-Feb)	Intradermal	1,813	359	RM732.12	RM262,831.08
Total in 3 Years		**24,043**	**7,867**		**RM5,759,588.04**
Average Total in 1 Year		**8,681**	**2,622**		**RM1,919,862.68**

Table 7.2: All subjects Received ID route Rabies Vaccine for PEP in Perak Region

Year	Route of Administration	Bite Cases	Vaccinated	Cost/Person	Total Cost/Year
2017	Intradermal	2	2	RM732.12	RM1,464.24
2018	Intradermal	0	0	0	0
2019 (Jan-Feb)	Intradermal	132	252	RM732.12	RM38,070.24
Total in 3 Years		**134**	**54**		**RM39,534.48**
Average Total in 1 Year		**45**	**18**		**RM13,178.16**

Table 7.3: Current PrEP Practice Among DVS and PBT

Year	Route of Administration	Pre-Exposure Subjects	Vaccinated	Cost/Person	Total Cost/Year
2018	Intradermal	250	250	RM488.08	**RM122,020.00**
Plan	Intradermal	359	359	RM488.08	**RM175,220.72**

4) Scenario 4: All subjects received IM route Rabies Vaccine either for PEP or PrEP

Table 8.1: All subjects Received IM route Rabies Vaccine for PEP in Sarawak Region

Year	Route of Administration	Bite Cases	Vaccinated	Cost/Person	Total Cost/Year
2017	Intramuscular	7,810	2,298	RM976.16	RM2,243,215.68
2018	Intramuscular	16,420	5,210	RM976.16	RM5,085,793.60
2019 (Jan-Feb)	Intramuscular	1,813	359	RM976.16	RM350,441.44
Total in 3 Years		**26,043**	**7,867**		**RM7,679,450.72**
Average Total in 1 Year		**8,681**	**2,622**		**RM2,559,816.91**

Table 8.2: All subjects Received IM route Rabies Vaccine for PEP in Perak Region

Year	Route of Administration	Bite Cases	Vaccinated	Cost/Person	Total Cost/Year
2017	Intramuscular	2	2	RM976.16	RM1,952.32
2018	Intramuscular	0	0	0	0
2019 (Jan-Feb)	Intramuscular	132	52	RM976.16	RM50,760.32
Total in 3 Years		**134**	**54**		**RM52,712.64**
Average Total in 1 Year		**45**	**18**		**RM17,570.88**

Table 8.3: Current PrEP Practice Among DVS and PBT

Year	Route of Administration	Pre-Exposure Subjects	Vaccinated	Cost/Person	Total Cost/Year
2018	Intramuscular	250	250	RM488.08	**RM122,020.00**
Plan	Intramuscular	359	359	RM488.08	**RM175,220.72**

5) Scenario 5: Optimum used of One Vial Rabies Vaccine via ID route for PEP or PrEP; 2 persons per vial

Table 9.1: Optimum used of One Vial Rabies Vaccine via ID route for PEP; 2 persons per vial (Optimum Used per Vial) – Sarawak Region

Year	Route of Administration	Bite Cases	Vaccinated	Average Cost/Person/Full Visit	Total Cost/Year
2017	Intradermal	7,810	2,298	RM597.12	RM1,372,181.76
2018	Intradermal	16,420	5,210	RM597.12	RM3,110,995.20
2019 (Jan-Feb)	Intradermal	1,813	359	RM597.12	RM214,366.08
Total in 3 Years		**26,043**	**7,867**		**RM4,697,543.04**
Average Total in 1 Year		**8,681**	**2,622**		**RM1,565,847.68**

Table 9.2: Optimum used of One Vial Rabies Vaccine via ID route for PEP; 2 persons per vial (Optimum Used per Vial) – Perak Region

Year	Route of Administration	Bite Cases	Vaccinated	Average Cost/Person/Full Visit	Total Cost/Year
2017	Intradermal	2	2	RM597.12	RM1,194.24
2018	Intradermal	0	0	0	0
2019 (Jan-Feb)	Intradermal	132	52	RM597.12	RM31,050.24
Total in 3 Years		**134**	**54**		**RM32,244.48**
Average Total in 1 Year		**45**	**18**		**RM10,748.16**

Table 9.3: Optimum used of One Vial Rabies Vaccine via ID route for PrEP; 2 persons per vial (Optimum Used per Vial)

Year	Route of Administration	Pre-Exposure Subjects	Vaccinated	Average Cost/Person/Full Visit	Total Cost/Year
2018	Intradermal	250	250	RM397.75	**RM99,437.50**
Plan	Intradermal	359	359	RM397.75	**RM142,792.25**

Table 10: Summary of Total Cost/Year

Scenario	Average Total Cost/Year (RM) (Sarawak + Perak)
Scenario 1 (Base Case)	RM2,350,877.99
Scenario 2	RM2,255,214.31
Scenario 3	RM1,933,040.84
Scenario 4	RM2,577,387.79
Scenario 5	RM1,576,595.84

Table 11: Percentage Difference

Scenario Comparison	Percentage Difference (%)
Scenario 1 vs Scenario 2	4.07%
Scenario 1 vs Scenario 5	**32.94%**
Scenario 2 vs Scenario 4	14.29%
Scenario 3 vs Scenario 4	25.00%
Scenario 4 vs Scenario 5	38.83%

DISCUSSION

In this report, two administration routes of rabies vaccine are considered; intradermal (ID) route and intramuscular (IM) route. Although the IM route is recommended and widely practices, the WHO has suggested the administration of rabies vaccine through intradermal is as potent as (≥2.5 IU/ml) intramuscular even with much lower dose; 0.1ml in ID versus 0.5ml in IM.[1] The ID route also reduce the visit cost and may improve patient's compliance.

This evaluation included direct costs involve during vaccination. The WHO concerned on the ID route especially for lower income country with high rate of rabies incidence.[1]The ID route of rabies vaccine was first started in Thailand in 1984. The used of ID route is an alternative to lower income country as it offers advantages through savings in costs, doses and time. Because of that, WHO strongly encouraged the vaccine manufacturer to submit a license variation application to national regulatory authorities for inclusion ID administration and WHO-recommended schedules as an approved use on the label.[11]

Since the outbreak in 2015, Ministry of Health (MOH) acknowledge the use of ID route which is more cost-saving than IM route. However, only Sarawak region obtained the special approval from Director General of Health and the approval should be renewed after a period of time. In view of potential cost saving of ID route, the MOH is looking forward for more cost-saving options to be practiced widely across Malaysia especially during the outbreak. Since the PrEP is one of successful step to control the spread of rabies, the MOH is planning to widen the practice as for now the PrEP depends on circumstances. One of the limitation of practicing PrEP is its high cost. Based on the CMA conducted, the ID route of rabies vaccine are cost-saving compared to IM route during PEP. The potential financial savings by changing from IM to ID route for rabies vaccination could be further utilised to enhance PrEP program.

CONCLUSION

Based on CMA, ID route of rabies vaccine either for PEP or PrEP was cost-saving compared to IM route. The optimum used of ID routes of rabies vaccine (one vial of rabies vaccine 0.5ml/vial was maximised for two persons) will save more compared to the base case (Scenario 1) especially during outbreak with a cost saving of approximately 32.94%.

ETHICS

This analysis is regarded as a secondary research with no direct involvement of patients or any other individual related to the topic of interest. The data for this project were extracted from the available local data or published literature. No application for approval from the MREC, Ministry of Health is needed.

RECOMMENDATION

Based on the above review, rabies vaccine administration through intradermal route is recommended during outbreak and prophylaxis as it may reduce the cost approximately at 32.94%. However, the intradermal technique requires prior training.

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32. Rabies Vaccines and Immunoglobulins: WHO Position. Summary of 2017 Updates. Available at: https://www.who.int/rabies/resources/who_cds_ntd_nzd_2018.04/en/ Accessed on 6 March 2019
33. Anothaisintawee T, Genuino AJ, Thavorncharoensap M. et al. Cost-Effectiveness Modelling Studies of All Preventive Measures Against Rabies: A Systematic Review. Vaccine. 2018
34. WHO Report. Rabies vaccines: WHO position paper, April 2018 – Recommendations. World Health Organization. Vaccine. 2018;36(37):5500-5503
35. Anothaisintawee T, Julienne Genuino A, Thavorncharoensap M et al. Cost-Effectiveness Modelling Studies of All Preventive Measure Against Rabies. A Systematic Review. Vaccine. 2018

9. APPENDIX

9.1. Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1946 to present

1. RABIES/ or RABIES VIRUS/
2. Rabies.tw.
3. Lyssa#.tw.
4. (Rabies adj virus#).tw.
5. 1 or 2 or 3 or 4
6. Humans/
7. human.tw.
8. 6 or 7
9. 5 and 8
10. Rabies Vaccines/
11. (Rabies adj1 vaccine$).tw.
12. Rabies human$ diploid cell$ vaccine$.tw.
13. 10 or 11 or 12
14. Injections, Intradermal/
15. intradermal.tw.
16. Intradermal rabies vaccine$.tw.
17. Intradermal injection rabies vaccine$.tw.
18. (Injection$ adj intradermal).tw.
19. 14 or 15 or 16 or 17 or 18
20. 13 and 19
21. Pre-Exposure Prophylaxis/
22. Pre-exposure.tw.
23. Pre exposure.tw.
24. (Pre exposure adj1 prophylax$).tw.
25. (Pre-exposure adj1 prophylax$).tw.
26. 21 or 22 or 23 or 24 or 25
27. Post-Exposure Prophylaxis/
28. (Post exposure adj1 prophylaxis).tw.
29. (Post exposure adj1 prevention).tw.
30. (Post-exposure adj1 prevention).tw.
31. (Post exposure adj1 prophylaxis).tw.
32. 27 or 28 or 29 or 30 or 31
33. 26 and 32
34. 20 and 33
35. 9 and 34

OTHER DATABASES		
EBM Reviews - Cochrane database of systematic reviews		
EBM Reviews - Health Technology Assessment		
PubMed		Rabies vaccine, intradermal rabies vaccine, pre-exposure, post-exposure
NHS economic evaluation database		
INAHTA		
FDA		
Others (Google Scholar, Google)		

9.2. Appendix 2

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomised controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

9.4. Appendix 3 EVIDENCE TABLE

EFFECTIVENESS
Evidence Table: Efficacy/Effectiveness
Question: Is it INTRADERMAL RABIES VACCINE effective for pre- and post-exposure rabies prophylaxis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Langedijk AC, de Pijper CA, Spijker R, Holman R, Grobusch MP & Stijnis C.Rabies Antibody Response after Booster Immunization: A Systematic Review and Meta-Analysis. Clin Infect Dis. 2018	SR and Meta-Analysis Obj: SR to summarize the published data on the boostability of rabies immunization to date MA and meta-regression to describe pre-booster seroconversion to rats (SCRs) and pre- and post-booster geometric titers (GMTs) and comparing IM and ID routes Methods: Selection criteria: rabies booster immunization more than 1 year after initial vaccination Short-term boostability: booster immunization 1-2 years after initial vaccination Long-term boostability: booster immunization more than 2 years after primary immunization		Total of 4912 subjects 36 (published between 1984-2014) studies of 31 trials included for qualitative analysis – 29 reported on short-term boostability and 7 on long-term boostability				Primary Outcome: percentage of participants with antibody levels ≥ 0.5 IU/mL before booster vaccination on day 365 or later after primary immunization and the same percentage immediately after booster immunization → SCR (percentage of seroconverted at day 14 and 21 after primary immunization) Secondary Outcome: GMT and antibody range before and after boostering at day 365 or later **RESULTS** The overall outcomes reported GMTs at pre- and post-booster vaccinations after IM and ID primary schedules on day 14 ➔ Overall findings, **GMTs were higher after IM primary schedules compared to ID** schedules ➔ More **GMTs dropped below 0.5 IU/mL after ID primary** vaccination ➔ **After booster administration both** IM and ID studies reported **GMTs above 0.5 IU/mL** ➔ **GMTs after booster doses** were **higher after boostering in IM compared to an ID primary** schedule ➔ Of 29 studies on 4200 subjects reporting **short-term boostability, all describe a GMT above or equal to 0.5 IU/mL after booster immunization** ➔ All studies except 1 described SCR of 100% Meta-analysis ➔ 19 studies on short-term	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							boostability were included in the MA Meta-analysis on SCRs ➔ **SCRs** MA included 17 studies (1504 subjects) – **percentage after ID immunization were generally lower than IM** – pooled percentage for ID (62%, 95% CI 47-76, I^2 = 96.44%) was **significantly lower (p = 0.005) than IM** (90%, 95% CI 80-100, I^2 = 99.13%) ➔ SCRs after booster of ID and IM were close to 100% therefore not eligible for MA Meta-analysis on **GMTs** ➔ Meta-analysis conducted on pre-booster (8 studies with total of 1660 subjects) and post-booster (10 studies with total of 1955 subjects) immunization ➔ Pre-booster GMTs • Mean value in ID group was 0.49 IU/mL (95% CI 0.23, 1.06, I^2 = 99.98%) compared to 1.44 IU/mL (95% CI 0.91, 2.25, I^2 = 99.98%) in the IM group • **GMTs pre-booster** were **significantly lower for ID** immunization **compared to IM** immunization **(p = 0.014)** ➔ Post-booster GMTs • **Mean value in ID** group was **17.64 IU/mL** (95% CI 13.77, 22.61, I^2 = 99.86%) and the **IM mean value was 59.87 IU/mL** (95% CI 64.64, 104.39, I^2 = 99.86%) • **After booster doses in both routes, the lower limits of all 95% CI were clearly above 0.5 IU/mL** • **GMTs post-booster** were **significantly lower for ID**	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							compared to IM (p = 0.003) SCRs on Day 7 & 14 • 8 studies (1226 subjects) measured antibodies post-booster on day 7 and 14 • 7 out of 8 studies showed that SCRs on 7 and 14 were 100% • 1 studies reported a lower SCR for both short (145/145, 98%) and long-term (267/275, 97%) boostability on day 7 • For all included studies, the GMT and antibody ranges were higher on day 14 compared to day 7 • 1 study followed their cohort for 10 years after a booster at year 1 → at end of the follow-up period, 73% (163/222) still had titres ≥ 0.5 IU/mL → antibody titres declined from the 1st year after booster immunization until year 10 → largest decline was seen after the 1st year but still above 0.5 IU/mL • 1 study followed up for 5 years after booster injection at year 1 → the SCR gradually decreased over the 5 years to 80% (69/86, IM route for both primary and booster doses) and 54% (48/89, ID route for both primary and booster doses) Abbreviated Schedules • 11 (38%) out of 29 studies on short-term boostability investigated abbreviated schedules even including 1 or 2 doses and schedules with different time intervals • In all divergent schedules, GMTs were above 0.5 IU/mL following 1 booster Multiples booster vaccinations • 2 studies showed that additional booster after 5 and 10 years resulted in a SCR of 100%	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							• 1 study demonstrated that participants who received multiple booster had significantly lower GMTs at day 14 compared to participants that received 1 single booster Conclusion • Booster response following ID and IM immunization are effective → **both induce adequate antibody levels according to the WHO** • PEP can safely be administered without the use of RIG after possible exposure a long time after a primary schedule • Abbreviated primary schedules containing 1 or 2 doses and schedules with different time intervals may also be boostable thus increased the number of individuals protected by rabies immunization → but still require more research	

Evidence Table: Efficacy/Effectiveness
Question: Is it INTRADERMAL RABIES VACCINE effective for pre- and post-exposure rabies prophylaxis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Preiss S, Chanthavanich P, Chen LH, Marano C, Buchy P, Van Hoorn R, Noordegraaf MV & Mukherjee P. Post-Exposure Prophylaxis (PEP) for Rabies with Purified Chick Embryo Cell Vaccine: a Systematic Literature Review and Met-Analysis. Expert Review of Vaccines. 2018	SR and MA Obj: To assess the immunogenicity, efficacy and safety of purified chick embryo cell culture rabies vaccine (PCECV) for PEP rabies by IM or ID administration MA conducted to compare immunogenicity according to the route of vaccine administration, study population and PEP regimen (number of dose and concomitant rabies immunoglobulin)	1	48 article included (33 intervention studies, 14 observational studies and 1 interventional and observational studies) Most of included studies estimated outcomes for more than one subgroup (55 estimated for immunogenicity, 10 for efficacy and 48 for safety) Intervention studies conducted in: Asia (Chia, India, Philippines, Thailand), Europe (Austria, Croatia, Chez Republic, Germany, Lithuania, Serbia) All observational studies: Asian countries	ID Purified Chick Embryo Cell vaccine (PCECV)	IM PCECV		**RESULTS** **Immunogenicity** • **Rabies virus neutralizing antibody GMT** - MA for RVNA levels could not be performed because of missing data Intramuscular - **All interventional studies using IM** of PCECV according to various vaccination schedules **reported RVNA GMTs ≥0.5 IU/mL on D14, D90 and D365** for all groups except 1 (RVNA GMT was 0.36 IU/mL at D14 in 14 adults) - GMT values at D14 varied greatly among age groups and with vaccination schedules and assay used to assess RVNA levels - **Observational studies on bite cases** in individuals of all ages also **reported RVNA GMTs ≥0.5 IU/mL on D14, D90 and D365** Intradermal - In **interventional studies using ID** administration of PCECV, **RVNA GMTs ≥0.5 IU/mL were reported n D14 and D90**, regardless of the regimen used → **6 studies reporting values ≥0.5 IU/mL up to D365** - RVNA GMT values **at D90 ranging from 4.9 to 17.7 IU/mL were collected from observational studies** • **Proportion of participants with rabies virus neutralizing antibody titers ≥0.5 IU/mL following IM administration of PCECV** - 17 interventional studies included in the MA - The overall estimated of the proportion of individuals with RVNA	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							titers ≥0.5 IU/mL at D14, irrespective of population was 99% (95% CI 97,100; I^2 = 71.6%; p<0.001) - Percentage of individuals with adequate RVNA titers at D14 among healthy volunteer (99% (95% CI 95,100%, I^2 = 71.6%, p <0.001), bite cases (99% (95% CI 95,100%, I^2 = 35.4%, p <0.19) and people at risk (96% (95% CI 95,100%, I^2 = 73.9%, p <0.001)) - The overall estimated on D7 (44%) and D90 (100%) - In Stratified analysis: based on reported dose potency performed on all populations, the percentage of vaccines with RVNA titers ≥0.5 IU/mL at D14 was ≥98% for doses of high and normal potency, and at day 7 titers ≥0.5 IU/mL were reached in 64% and 15% of the people vaccinated with high potency and normal potency PCECV doses - Stratified analysis based on number of doses provided to each vaccine, irrespective of population → overall estimated for the proportion of individuals with RVNA titers ≥0.5 IU/mL on D 14 for 4-, 5- or 6-dose vaccination schemes were >97% - No significant differences were found between the 4-, 5- and 6-dose schemes - Overall estimates for the proportion of vaccines with adequate RVNA levels on D14 were → for no RIG administered (100% 95% CI 100,100, I^2 = 02%, p = 0.60), for ERIG (77% 95% CI 37,100, I^2 = 92.6%, p<0.001) and for HRIG (90% 95% CI 69,100, I^2 = 77.7%, p<0.001) - For healthy volunteers and people at risk combined, the estimated rate of adequate RVNA levels for PCECV with no additional RIG was 100% at D14 and 50% at D7	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							• **Proportion of Participants with Rabies Virus Neutralizing Antibody Titers ≥0.5 IU/mL following ID Administration of PCECV** - 14 interventional studies included in MA - Overall proportion of participants with adequate RVNA levels on D14 was 100% (95% CI 99,100; I^2 = 0.0%; p = 0.91) - Overall estimates for ➢ Healthy volunteers (100% (95% CI 99,100; I^2 0.0%; p = 0.63), ➢ Bite cases (100% (95% CI 99,100; I^2 0.0%; p = 1.00) and ➢ People at risk (100% (95% CI 99,100; I^2 0.0%; p = 0.75) - Stratified analysis by **dose potency** → on D14 only in combined populations → estimated 100% for both normal and high potency PCECV dose - Stratified analysis by **number of doses administered** → overall percentages of individuals with adequate immune response to vaccination of ➢ 8-doses scheme → administered in 4-5 visits (100% (95% CI 99,100%; I^2 = 0.0%; p = 0.85)), ➢ 10-doses scheme → 2-2-2-2-2 or 4-4-1-1 (99% (95% CI 93,100%; I^2 = 41.8%; p = 0.16)), and ➢ 12-doses scheme → administered in ≥3 visits (100% (95% CI 99,100%; I^2 = 0.0%; p = 1.00)). - Stratified analysis of RIG administration: overall estimates on D14 for ➢ No RIG: 100% (95% CI 100-100%, I^2 = 0.0%; p = 0.99) ➢ ERIG: 100% (95% CI 96-100%, I^2 = 51.7%; p = 0.10) ➢ HRIG: 100% (95% CI 98-100%, I^2	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							= 0%; p = 0.60 ➢ 1 study in ERIG or HRIG was administered within the same study population reported 99% (95% CI 95-100%) of subjects had RVNA titres ≥0.5 IU/mL at D14 - 5 observational studies reported on the adequacy of immune response for PCECV → 3 studies reported adequate RVNA levels in GMTs from D14 and 1 study reported adequate RVNA levels throughout the whole study period (3 years) → another 1 study RVNA titers ≥0.5 IU/mL were reported after 2 months up to 12 months - MA to compare ID and IM routes could not be done due to difference in duration of measurements and difference in populations • **Assessment Methods for Rabies Virus Neutralizing Antibody Titers** - RVNA assessments using ➢ Rapid fluorescent focus inhibition test (RFFIT) in 29 studies (24 interventional and 5 observational studies) ➢ Mouse neutralization test (MNT) in 11 studies (6 interventional and 5 observational studies) ➢ Enzyme-linked immunosorbent assay (ELISA) in 1 interventional study ➢ Method that employing an interventional reference serum containing 2 IU/mL of RVNA to calculate the titer of RVNA sample in one interventional study ➢ In vitro serum neutralization test as RVNA assay in 1 observational study and one study not reported the type of assay used ➢ Studies that used RFFIT and MNT showed no difference	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							between the tests for the reported RVNA titers at D14 **Efficacy** Intramuscular Rabies (PCECV) Injection - 2 interventional and 4 observational trials reported 100% survival throughout the study period Intradermal Rabies (PCECV) Injection - 1 interventional study reported bite cases with 100% survival rate during the study period - 4 observational studies reported 100% survival after 1 year, 3 years and throughout study period India - Observational study with 32 patients with exposure to laboratory-confirmed rabid dogs received wound care and PCECV by multisite ID administration and HRIG or ERIG was also administered to 22 patients - Source of the exposure was 12 dogs, 9 of which were stray and 3 were unimmunized pets - All patients were followed up for 3 years and were alive and doing well Thailand - Between 1996-2001 → estimated 587,528 dogs (8.9% stray digs, 91.1% house dos and 71.0% vaccinated for rabies) - During the same period, 8157 bite cases reported of which 51% were category III exposures; although 3.0% received RIG, all of the patients who received ID route vaccine survived → 2 deaths were reported among poor subsistence farmers who did not seek PEP after dog bites Special Population - AIDS patient, Pregnant women and - Children	

Evidence Table: Efficacy/Effectiveness
Question: Is it INTRADERMAL RABIES VACCINE effective for pre- and post-exposure rabies prophylaxis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
3. Recuenco S, Warnock E, Osinubi MOV & Rupprecht CE. A Single Center, Open Label Study of Intradermal Administration of an Inactivated Purified Chick Embryo Cell Culture Rabies Virus Vaccine in Adult. Vaccine. 2017	Single centre- Open-label non-randomized Control Trial Obj: To determine the immunogenicity of PCEC to induce adequate levels of RVNA in subjects following receipt of three 0.1 mL (0.25 IU/mL) ID doses, as recommended by WHO, compared to three (2.5 IU/mL IM doses, or single booster doses To compare the relative safety of PCEC administered via the ID route, in comparison with the IM route Methods: Settings: enrolment at 2 occupational health clinic (OHC) at CDC in Atlanta (PrEP administration) Follow-up site visit at Royal Campus OHC and Chamblee Campus OHC Immunological Analysis: Blood samples were collected prior to each vaccination (Days 1,7 and 21) and on Days 14, 60, 120 and 160 after 1st vaccination) – the rabies virus neutralizing antibodies (RVNA) tested with RFFIT		128 individuals Female (53%) Male (47%) Age 20 to 60 years old Patients were subgroup into: i. PrEP IM ii. PrEP ID iii. Booster IM iv. Booster ID	PCECV rabies vaccine Three (0.25 IU/mL) ID doses	PCECV rabies vaccine Three (2.5 IU/mL IM doses, or single booster doses		Primary Outcome: proportion of subjects who developed RVNA titres of at least 1:5 (~ 0.1 IU/mL) or highest against rabies virus, 14 days after completion of the vaccination schedule and frequencies and severities of AEs Secondary Outcome: Serum VNA titers measured 2, 4 and 5 months after the receipt of full vaccination schedule **RESULTS** - All participants in all groups achieved levels of RVNA ≥1:5;~ 0.1 IU/mL 14 days after completion of their correspondent PrEP or booster vaccination regimen, indicating optimal seroconversion PrEP - VNA antibody levels ≥1:5 were observed in the PrEP group before the time of 3rd dose of vaccine on day 21 - GMT values of VNA for each PrEP group peaked at 14 days after 3rd dose of vaccine and decrease slowly until the end of the follow-up, 160 days after vaccination was completed but all maintained values over 0.5IU/mL → the GMT values of VNA for the PrEP IM group were approximately 2-fold higher than the ones for the PrEP ID group → the difference were svtatistically confirmed by p-values from T-test for all the visit except for base line D0 (p = 0.408), D7 (p = 0.001), D21 (p = 0.002) → 95% CI does not delineate the GMTs and overlapping of the CI is observed Booster - Peak VNA GMTs were observed at	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							day 14 for both Booster Group - Rapid increase in VNA in both ID and IM booster group from day 0 to 14 showed only a gradual decline over the 160 days of follow up - At day 160, VNA GMTs were ~ 5-fold higher than the starting levels in those receiving the ID revaccination and approximately 10-fold higher than starting levels in those receiving IM - GMT of NVA levels for the Booster IM group were between 2- and 3-fold higher than the GMT values for the Booster ID group → statistically significant by T-test analysis → non-overlapping 95% Cis of the GMTs were only demonstrated at day 14 post booster immunization Efficiency Vaccine Vials Used for Multiple ID uses - Maximum number of doses extracted was 6 doses with average of 4 doses per vial for the groups of vials used for ID - The time of opening between opening and discarding vials for IM (one time use) was 1 – 113 min, with mean of 22 min - For vials used multiple times, the time was between 21 minutes to 8 hrs and 41 min with average of 5 hrs and 11 min - The ranges of time the vial was 'in use' by number of doses extracted per vial were narrower as a larger number of doses were extracted - No damage observed in the vial stoppers, but needle punctures were visible in 32 (20%) of the 161 vials used, including 4 vials used only for 1 dose Conclusion - Administration of RV Pre-EP via the ID route is feasible and effective.	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							- Such investigational new drug (IND) use may be considered when large at risk groups require primary or booster vaccinations in the event of vaccine shortages. - The public would benefit from specific recommendations for ID use as elaborated by manufactures, regulatory agencies, and specific reviewing groups, such as Advisory Committee on Immunization Practices (ACIP) - Moreover, these data substantiate and underscore the utility of the ID route for rabies immunization for at risk populations in the developing world, as a cost-effective alternative to IM administration	

Evidence Table: Efficacy/Effectiveness
Question: Is it INTRADERMAL RABIES VACCINE effective for pre- and post-exposure rabies prophylaxis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
4. Jonker EFF, & Visser LG. Single Visit Rabies Pre-Exposure Priming Induces a Robust Anamnestic Antibody Response After Simulated Post-Exposure Vaccination: Results of a Dose-Finding Study. J of Travel Med. 2017; 1-8	RCT Non-blinded comparative randomized clinical trial Obj: To determine the optimal PrEP vaccination regimen that would require only a single visit to the clinic in order to produce an adequate memory response in all subjects after 1 year Method: Setting: Travel Clinic of Department of Infectious Diseases at Leiden University Medical Centre, Netherlands		30 subjects Patients: Volunteers between 18 and 31 years' old and predominantly female (70%) Randomly assigned to 4 regimens for primary rabies vaccination using computer-generated permuted block randomization: 4 groups A: 1-site 0.5 mL IM (standard dose) B: 1-site 0.1 mL ID (equivalent to 20% of standard dose) C: 2-site 0.1 mL ID (40% standard dose) D: 3-site 0.1 mL ID (60% of standard dose)	ID purified Vero cell rabies (PVRV) B: 1-site 0.1 mL ID (equivalent to 20% of standard dose) C: 2-site 0.1 mL ID (40% standard dose) D: 3-site 0.1 mL ID (60% of standard dose) All injections were given at same visit on a single day Multisite injections were given at distinct body sites to address maximum number of lymph node stations	IM purified Vero cell rabies (PVRV) Group A: 1-site 0.5 mL IM (standard dose)	Nov 2014 – March 2016 After 1 year, all subjects received 2 standard doses on day 0 and day 3 to simulate rabies PEP	**RESULTS** - All subjects completed the study including the simulated PEP 1 year after primary vaccination 1 months after priming (experimental primary vaccination) - Overall 93% (95% CI 84 – 100%) seroconversion rate for the 1-visit priming schedules ➢ Group A: 9 out of 10 subjects seroconverted (1-IM) ➢ Group B: 9 out of 10 in arm B (1/5th-ID). ➢ Group C: 5 out of 5 subjects seroconverted (2/5th-ID) and ➢ Group D: 5 out of 5 (3/5th-ID) - 1 month after priming, GMT were not different between groups, and there was no dose-response relationship with regards to antigen dose at priming 1 year after primary vaccination - 8 out of 30 subjects still had RVNA titer >0.5 IU/ml before simulated PEP: ➢ Group A: 3 out of 10 ➢ Group B: 2 out of 10 ➢ Group C: 1 out of 5 ➢ Group D: 2 out of 5 One week after 1st booster dose - 30 subjects seroconverted within 1 week of the 1st booster dose even in those who did not seroconvert after primary vaccination → all experimental study arms satisfied the primary endpoint At 7 days after revaccination - GMTs increased 251-fold in Group A - GMTs 48- to 86-fold in the ID groups - Difference in fold increase was significant ($p < 0.03$) for Group A	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							compared to Group C and D Dose-response relationship - 1-IM Group A showed the highest GMT post-booster - No dose-response relationship was found in the study when all groups were compared - Serology performed at day 3 post-booster did not show a difference in GMT from the pre-booster baseline RVNA Curve - RVA curves of RVNA titers a day 7 post booster showed the highest titers in the 1-IM group, $p < 0.0015$ for each ID group vs IM - No difference between ID group was found - No correlation between local reactogenicity and RVNA titer at day 28 post-primary or day 7 booster Wheal Diameter - Average wheal diameter after ID injection was 9.2 mm Others - 2 subjects finished the study outside the re-defined time limits (4 months early and 4 months late, both from Group A) → removing their data from analysis did not change the results Conclusion - Effective rabies PrEP for travellers may be achieved in a single visit with 100% booster response after 1 year even in those who do not seroconvert after the priming dose - Required further study with adequate powered and should include standard IM PrEP IM schedule as a control arm	

Evidence Table: Efficacy/Effectiveness
Question: Is it INTRADERMAL RABIES VACCINE effective for pre- and post-exposure rabies prophylaxis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
5. Soentjens P, Andries P, Aerssens A, Tsoumanis A, Ravinetto R, Heunninckx W, van Loen H, Brochier B, Van Gucht S, Van Damme P, Van Herrewege & Bottieau E. Pre-Exposure Intradermal Rabies Vaccination: a Non-Inferiority Trial in Healthy Adults on Shortening the Vaccinaation Schedule from 28 to 7 days. Clin Infect Dis. 2019;68(4):607-614	RCT Obj: To demonstrate non-inferiority of the 2-visit (2ID) schedule compared to the 3-visit (3ID) → adequate rabies antibody titres above 0.5 IU/mL 7 days following a booster vaccine injectuin (0.1 mL of human diploid cell culture vaccine (HDCV) administered 1 to 3 years after primary vaccination Other outcomes, RFFIT levels above 10.0 IU/mL, GMT of rabies antibody and fold increases compared to baseline values 7 days after a booster injection and to assess the percentage of subjects with rabies antibody levels above 0.5 IU/mL, the GMT and fold increases compared for both study groups on day 35 after the start of primary vaccination		500 patients • Recruited from the Belgian Armed Forces • Age between 18-47 years Randomization process • Block randomization to 1 of the 2 ID PrEP schedules • Intervention Group: Intradermal (ID) group • Control group: Intramuscular (IM) group	HDCV rabies Merieux 1ml vaccine for rabies → injected ID on the forearm ID booster dose of 0.1 mL for both groups was planned at least 1 year later **2x2x0.1 ID schedule** (2ID); double-dose 2-visit; 2 ID injections (of 0.1 mL in 2 separate injection sites (2 x 0.1 ID)0 on day 0 and 2 injections (in separate sites (2 x 0.1 ID)) on day 7	HDCV rabies Merieux 1ml vaccine for rabies → injected ID on the forearm **3 x 0.1 ID schedule** (3 ID), single-dose 3 visits; 1 intradermal injection (a dose of 0.1 mL (0.1 ID)) on days 0, 7 and day 28	RFFIT on day 0 (the day of the primary vaccination), on days 35 after the start of the primary vaccination, on the day of the booster vaccine injection and 7 days later	**RESULTS** 3 ID schedules • 240 subjects completing 3 ID schedules → 200 (83%) received booster→185 (77%) subjects were included in per-protocol analysis 2 ID schedules • 242 subjects completing 2 ID schedules → 211 (87%) received booster → 183 (75%) subjects were included in per-protocol analysis Adequate RFFIT > 0.5 IU/mL at day 7 after a single booster (ITT analysis) 3 ID schedules • 54% of 200 subjects in the 1st year following primary vaccination, 38% in the 2nd year and 8% in the 3rd year 2 ID schedules • 59% of 211 participants in the 1st year, 35% in the 2nd year and 6% in the 3rd year (Per-protocol analysis) • All subjects (100%) in both groups displayed RFFIT >0.5 IU/mL on day 7 fllowing a single 0.1 ID booster dose • The difference of the 2 groups ranged between -2 and 2% RFFIT >10 IU/mL at day 7 after a single booster • RFFIT >10 IU/mL following a single O.1 ID booster dose → proportion of participants reaching this level in the 2ID schedule was higher than in the 3 ID schedule (96% vs 83%) with difference if 13% (95% CI 7,9) Other serology results GMT • 2 ID exhibited GMT 37 IU/mL (95% CI 33,42) following the booster vaccination offered 1 to 3 years later	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							compared to GMT 25 IU/mL (95% CI 22,29) for the 3 ID group (p < 0.001) • GMT values on the day if booster injection in the 2 ID schedule were higher (3.4 IU/mL, 95% CI 2.9,3.9) compared to these of the 3ID schedule (2.0 IU/mL, 1.7, 2.4) (p < 0.001) • 2ID schedule exhibit a higher slope following the booster dose (46.4, 95% CI 39.1, 53.6) compared to the 3 ID schedule (35.7, 95% CI 26.1, 45.3) • Overall GMTs trend significantly higher following primary vaccination for 3 ID schedule and higher following the booster dose for the 2 ID schedule • Male gender (p < 0.0001), age 20-30 years (P = 0.0021) and between 30 and 40 years (p = 0.0023) and a higher pre-booster GMT (p < 0.0001) were associated with improved post-booster results in favour of the 2 ID schedule • Post-booster GMT levels were also higher in favour of the 2 ID schedule when analysed by booster dose timing → this were only significant when the interval between PrEP and PEP was greater than 25 months (p = 0.0002) Day 35 results after primary vaccination • All subjects in the per-protocol analysis set attained RFFIT results > 0.5 IU/mL 35 days after starting primary vaccination • More subjects exhibit rabies antibody titers >10 IU/mL in the 3ID group 982%) compared to the 2ID group (70%) (difference -12%, 95% CI -19, -4.3) Conclusion • Safe and effective PrEP for travellers or people living in endemic rabies	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							region may be achieved with double-dose 2-visit 0.1 ID regimen with 100% adequate antibody response following a booster injection of 0.1 ID 1 to 3 years after primary vaccination	

Evidence Table: Efficacy/Effectiveness
Question: Is it INTRADERMAL RABIES VACCINE effective for pre- and post-exposure rabies prophylaxis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
6. Kerdpanich P, Chanthavanich P, De Los Reyes MR, Lim J, Yu D, Ama MC, Mojares Z, Casula D, Arora AK & Pellegrini M. Shortening Intradermal Rabies Post-Exposure Prophylaxis Regimens to 1 Week: Results from a Phase III Clinical Trial in Children, Adolescents and Adults. PLOS Negl Trop Dis. 2018; 12(6): e0006340	RCT (Phase III) Controlled, open-label, multi-center study Setting: 4 centres in Philippines and 2 centers in Thailand Study Period Jun 2014 and August 2015 Obj: To assess non-inferiority of the immune response of the 4-site/1-week ID PEP regimen to that of the currently recommended 2-site/TRC ID regimen of PCECV, with or without HRIG administration → measured by the percentage of participants with rabies virus neutralizing antibody (RVNA) concentrations ≥0.5 international units (IU)/mL in the whole study population, at D49 To compare antibody responses at D7, D14, D90, D180 and D365 in terms of RVNA GMCs and percentage of participants with RVNA concentrations ≥0.5 IU/mL following each PCECV Non-inferiority was demonstrated if the lower		885 Healthy individuals ≥1 year of age, never received any rabies vaccines or RIG, had no previous exposure to rabies and no history of allergy or contraindications Age strata: 1-5 years, 6-17 years and ≥18 years Groups: Age <18 years: randomly assigned (1:1) to: ➢ Group A1: 4-site/1-week ID regimen or ➢ Group B1: 2-site/TRC regimen Adults ≥18 years: randomly assigned into 4 groups (2:1:2:1) ➢ Group A1: 4-site/1-week ID regimen alone ➢ Group A2: 4-site/1-week ID regimen with concomitant HRIG administration at 1st visit ➢ Group B1: 2-site/TRC ID regimen alone ➢ Group B2: 2-site/TRC Id regimen with concomitant HRIG administration at 1st visit	4-site/1-week ID PEP regimen of PCECV with or without HRIG Potency of PCECV 6.87 IU/mL with final volume 1mL with sterile water Group A1 and A2: received 4 injections of 0.1mL of PCECV	2-site/TRC ID regimen of PCECV with or without HRIG Group B1 and B2: received 2 injections of 0.1mL of PCECV		**RESULTS** Demographics - 885 enrolled participants → 875 completed study - Compliance: high (98%) in groups A1, A2 and B1 and all participants in Group B2 Immunogenicity - At D49: RVNA concentrations ≥0.5 IU/mL ➢ Group A1 + Group A2: 99% (95% CI: 98%±100%) ➢ Group B1 + Group B2: 100% (95% CI: 99%±100%) ➢ LL of the 2-sided 95% CI on the between-group difference was -2.4% which is above the pre-specified non-inferiority margin - In the whole population, for both vaccination regimens → RVNA concentrations ≥0.5 IU/mL by D14 and the vast majority of them (90% in Group A1 + Group A2 and 83% in Group B1 + Group B2), maintained adequate RVNA concentrations at D365 after first vaccination - RVNA GMCs peaked at D14 and declined at subsequent time points - At D49, the RVNA GMC ratio (Group A1 + Group A2 over Group B1 + Group B2) was 0.46 (95% CI: 0.37±0.58) - LL of the 95% CI was below the pre-specified non-inferiority margin - At D365 higher immune response was observed in the groups receiving the 4-site/1-week regimen than in those receiving the 2-site/TRC regimen Not receiving HRIG (Group A1 & B1) - All study participants achieved adequate RVNA levels by D14	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	limit (LL) of the 2-sided 95% CI around the difference [(Group A1 + Group A2) – (Group B1 + Group B2)] in the percentage of participants with RVNA concentrations -0.5 IU/mL was greater than -5% (> 0.667) Methods *Immunogenicity assessment*: Blood samles were collected at D0, D7, D14, D49, D90, D180 and D365 → RVNA level were assessed using RFFIT → RVNA ≥0.5 IU/mL by D14 (WHO)						- Higher proportion of participants in Group A1 (95%) than in Group B1 (87%) maintained adequate neutralizing antibody levels for 1 year following first vaccination - RVNA GMCs peaked at D14 and then declined up to D365, with higher values being observed in Group A1 than in Group B1 at D14 and D365 At all-time points except D14 - The percentage of adults with adequate RVNA concentrations was lower in Group A2 than in group A1 - RVNA GMCs were consistently lower in Group A2 than in Group A1 Receiving HRIG (Group A2 & B2) - All time points (except D90) Comparable percentages of adults with RVNA concentrations ≥0.5 IU/mL for groups A2 and B2 - At D90: adequate RVNA levels was significantly lower in Group A2 than in Group B2 - RVNA GMCs peaked in both groups at D14: significantly higher GMC was observed in Group A2 than in Group B2 - RVNA levels declined in both groups at subsequent time points - The same trend as described for the overall population was observed in the different age strata evaluated, including in the youngest participants (children 1±5 years of age). Conclusion - The administration of PCECV according to a 4-site/1-week ID regimen for rabies PEP was non-inferior to that according to a 2-site/TRC ID regimen in terms of percentages of participants with RVNA concentrations ≥0.5 IU/mL at D49.	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							- The elicited immune responses peaked at D14, and subsequently declined up to D365	

Evidence Table: Efficacy/Effectiveness
Question: Is it INTRADERMAL RABIES VACCINE effective for pre- and post-exposure rabies prophylaxis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
7. Angsuwatcharakon P, Khomvilai S, Limsuwan K, Ratananpinit N, Khamcat A, Sanitnai T & Tantawichen. Immunogenicity and Safety of WHO-approved TRC ID Regimen with a Chromatographicall y Purified Vero Cell Rabies Vaccine with or Without Rabies Immunoglobulin in Children. Expert Review of Vaccines. 2017; 19:33	Pre- and post-intervention study Obj: To assess the immunogenicity of chromatographically purified Vero cells Rabies Vaccine (CPRC) when administered ID for PEP in paediatric patients Methods:		39 subjects Non-immunized patients aged less than 15 years Who had possible rabies exposure and classified as WHO categories II or III Recruited at outpatient rabies immunization clinic of Queen Saovabha Memorial Institute, Thai Red Cross Society	ID rabies vaccine 2-site ID Thai Red Cross Regimen (TRC-ID; 2-2-2-0-2-0) using two 0.1mLID doses of CPRV with or without RIG for children in Thailand	-	1 year (30 minutes 3 days after vaccination for adverse reactions)	**RESULTS** - 25 patients (64.1%) with severe bite wounds (rabies exposure HWO category III) received rabies immunoglobulin (11 cases received equine rabies immunoglobulin and 14 cases received human rabies immunoglobulin (due to positive skin test or were younger) concomitant with rabies vaccine on day 0 - Prior to rabies vaccination (day 0), all of paediatric patients showed undetectable Nab titers. - All patients had reached an adequate immune response for rabies (Nab titers above 0.5 IU/mL) on: ➢ Days 14 after PEP GMTs of Nab titers in patients: • Received the TRC-ID regimen **with** RIG were 16.17 IU/mL (range 4.00 - 65.40 IU/mL) or • Received the TRC-ID regimen **without** RIG and 14.14 IU/mL (range 2.23 - 39.74 IU/mL) ➢ Days 90 after PEP. GMTs of Nab titers in patients: • Received the TRCID regimen **with** RIG were 4.37 IU/mL (range 0.77-14.67 IU/mL) or • Received the TRCID regimen **without** RIG and 9.48 IU/mL (range 2.18-23.60 IU/mL) Conclusion - The available and economical TRC-ID regimen with CPRV should be selected for PEP in patients living in middle- and low-income countries. Intradermal vaccination with CPRV is as safe and immunogenic as the WHO-prequalified PVRV in children	

SAFETY

Evidence Table: Safety
Question: Is it INTRADERMAL RABIES VACCINE safe for pre- and post-exposure rabies prophylaxis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
8. Preiss S, Chanthavanich P, Chen LH, Marano C, Buchy P, Van Hoorn R, Noordegraaf MV & Mukherjee P. Post-Exposure Prophylaxis (PEP) for Rabies with Purified Chick Embryo Cell Vaccine: a Systematic Literature Review and Met-Analysis. Expert Review of Vaccines. 2018	SR and MA)	1	48 article included (33 intervention studies, 14 observational studies and 1 interventional and observational studies) Most of included studies estimated outcomes for more than one subgroup (55 estimated for immunogenicity, 10 for efficacy and 48 for safety) Intervention studies conducted in: Asia (Chia, India, Philippines, Thailand), Europe (Austria, Croatia, Chez Republic, Germany, Lithuania, Serbia) All observational studies: Asian countries	ID Purified Chick Embryo Cell vaccine (PCECV)	IM PCECV		**RESULTS** Intramuscular PCECV Injection - Most frequent reports locals AEs in 15 interventional studies were itching, erythema and pain - Most common reported systemic AEs were myalgia, headache, fever or having a feverish feeling - 1 study reported severe incidence of local and systemic AEs: 15 – 16% - 4 studies reported no serious AEs - From 7 observational studies → 5 studies reported pain as most common local AEs and other AEs headache and fever Intradermal PCECV Injection - Most frequently reported AEs from 16 interventional studies were local AEs (erythema, itching, induration, lymphadenopathy and pain) and systemic AEs (headache and fever or having feverish feeling ID vs IM - Erythema, induration and lymphadenopathy were more frequently reported for ID compared with IM - In study conducted among healthy hospital staff, veterinary students and patients with possible risk of infection → pain was more frequently reported in the IM group than ID group ($p < 0.001$), however ID caused more local irritation, erythema and induration (92%) compared with IM vaccination (66%) ($p < 0.02$)	

Evidence Table: Safety
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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
9. Recuenco S, Warnock E, Osinubi MOV & Rupprecht CE. A Single Center, Open Label Study of Intradermal Administration of an Inactivated Purified Chick Embryo Cell Culture Rabies Virus Vaccine in Adult. Vaccine. 2017	Single centre- Open-label non-randomized Control Trial Obj: To determine the immunogenicity of PCEC to induce adequate levels of RVNA in subjects following receipt of three 0.1 mL (0.25 IU/mL) ID doses, as recommended by WHO, compared to three (2.5 IU/mL IM doses, or single booster doses To compare the relative safety of PCEC administered via the ID route, in comparison with the IM route		128 individuals Female (53%) Male (47%) Age 20 to 60 years old Patients were subgroup into: i. PrEP IM ii. PrEP ID iii. Booster IM iv. Booster ID	PCECV rabies vaccine Three (0.25 IU/mL) ID doses	PCECV rabies vaccine Three (2.5 IU/mL IM doses, or single booster doses		**SAFETY** - No serious AEs were reported - Most reported were local and mild - Most frequent local complained were ➢ Erythema (61%), ➢ Induration (40%) and ➢ Tenderness (36%) at injection site - Most frequent systemic AEs were ➢ Headache (19%) ➢ Fatigue (18%) ➢ Fever (11%) ➢ Insomnia (8%) - 7 days after the first vaccine dose, all groups except the Booster Group had over 90% of participants reporting at least 1 AE - Erythema (80%) and induration (58%) were the most frequent complaints among ID Groups participant → markedly lower in IM Groups (erythema 15% and induration 8%) - 14 days after vaccination, all participants in the PrEP ID group had at least 1 AE compared to only 67% of the participants in the PrEP IM - In the Booster Group, participants in ID arm presented more AEs (20/31) than in IM arm (8/33) → erythema was the main complaints in ID arm which was almost none in IM arm	

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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
10. Jonker EFF, & Visser LG. Single Visit Rabies Pre-Exposure Priming Induces a Robust Anamnestic Antibody Response After Simulated Post-Exposure Vaccination: Results of a Dose-Finding Study. J of Travel Med. 2017; 1-8	RCT Non-blinded comparative randomized clinical trial Obj: To determine the optimal PrEP vaccination regimen that would require only a single visit to the clinic in order to produce an adequate memory response in all subjects after 1 year Method: Setting: Travel Clinic of Department of Infectious Diseases at Leiden University Medical Centre, Netherlands		30 subjects Patients: Volunteers between 18 and 31 years' old and predominantly female (70%) Randomly assigned to 4 regimens for primary rabies vaccination using computer-generated permuted block randomization: 4 groups A: 1-site 0.5 mL IM (standard dose) B: 1-site 0.1 mL ID (equivalent to 20% of standard dose) C: 2-site 0.1 mL ID (40% standard dose) D: 3-site 0.1 mL ID (60% of standard dose)	ID purified Vero cell rabies (PVRV) B: 1-site 0.1 mL ID (equivalent to 20% of standard dose) C: 2-site 0.1 mL ID (40% standard dose) D: 3-site 0.1 mL ID (60% of standard dose) All injections were given at same visit on a single day Multisite injections were given at distinct body sites to address maximum number of lymph node stations	IM purified Vero cell rabies (PVRV) Group A: 1-site 0.5 mL IM (standard dose)	Nov 2014 – March 2016 After 1 year, all subjects received 2 standard doses on day 0 and day 3 to simulate rabies PEP	**RESULTS** - No serious AE - AEs occurred after both primary and booster vaccination - After primary vaccination → 12 out of 30 subjects did not report any side effects → 8 subjects reported: ➢ Localized erythema (only ID groups (11/30) ➢ Myalgia (8/30) ➢ Fatigue (6/30) - In the ID groups, erythema of around 5mm at site of injection for the 1st few days -->< in some instance a small red spot remained until 4 weeks after injection - After 1 year, no evidence of ID injection would be found on the skin of any the subjects - After booster vaccination, myalgia occurred in 8/30 subjects with 1 subjects reporting swollen axillary lymph nodes and another reporting fatigue	

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11. Soentjens P, Andries P, Aerssens A, Tsoumanis A, Ravinetto R, Heunninckx W, van Loen H, Brochier B, Van Gucht S, Van Damme P, Van Herrewege & Bottieau E. Pre-Exposure Intradermal Rabies Vaccination: a Non-Inferiority Trial in Healthy Adults on Shortening the Vaccinaation Schedule from 28 to 7 days. Clin Infect Dis. 2018	RCT		500 subjects	HDCV rabies Merieux 1ml vaccine for rabies → injected ID on the forearm ID booster dose of 0.1 mL for both groups was planned at least 1 year later **2x2x0.1 ID schedule** (2ID); double-dose 2-visit; 2 ID injections (of 0.1 mL in 2 separate injection sites (2 x 0.1 ID)0 on day 0 and 2 injections (in separate sites (2 x 0.1 ID)) on day 7	HDCV rabies Merieux 1ml vaccine for rabies → injected ID on the forearm **3 x 0.1 ID schedule** (3 ID), single-dose 3 visits; 1 intradermal injection (a dose of 0.1 mL (0.1 ID)) on days 0, 7 and day 28	Safety: followed up until 7 and 28 days respectively following the completion of the primary vaccination and booster vaccination	RESULTS - 1 serious AE (reversible diplopia and hemianopsia) occurred during the primary vaccination session 14 days after receiving the final rabies vaccine injection (3ID schedule) - 2 serious AE (1 case of oesophagitis and another with dypsnea, angioedema and urticarial) occurred following a booster dose (2ID schedule) - Local irritation at the injection site (mild and transient) following primary vaccination tended to occur more frequently in 3ID compared to the 2ID schedule (51.8% vs 43.4%, p = 0.07) - Local irritiation was more often observed following the booster does in 2ID group (38.8% vs 48.8%, p = 0.03) - Systemic discomfort related to injection was very low and did not differ significantly between the 2 groups (3ID vs 2ID) following primary vaccination (14.5% vs 11.6%, p = 0.42) or booster injection (5.4% vs 5.8%, p = 1)	

Evidence Table: Safety
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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
12. Kerdpanich P, Chanthavanich P, De Los Reyes MR, Lim J, Yu D, Ama MC, Mojares Z, Casula D, Arora AK & Pellegrini M. Shortening Intradermal Rabies Post-Exposure Prophylaxis Regimens to 1 Week: Results from a Phase III Clinical Trial in Children, Adolescents and Adults. PLOS Negl Trop Dis. 2018; 12(6): e0006340	RCT (Phase III) Controlled, open-label, multi-center study Setting: 4 centres in Philippines and 2 centers in Thailand Study Period Jun 2014 and August 2015		Healthy individuals ≥1 year of age, never received any rabies vaccines or RIG, had no previous exposure to rabies and no history of allergy or contraindications ➢	4-site/1-week ID PEP regimen of PCECV with or without HRIG Potency of PCECV 6.87 IU/mL with final volume 1mL with sterile water Group A1 and A2: received 4 injections of 0.1mL of PCECV	2-site/TRC ID regimen of PCECV with or without HRIG Group B1 and B2: received 2 injections of 0.1mL of PCECV		**SAFETY** Reactogenicity and Safety 4-site/1 week regimen Group (GA1 & A2) → At least 1 solicited AE was reported - 57% (Group A1) and 65% (Group A2) of participants 2-site/TRC regimen (GB1 & B2) → At least 1 solicited AE was reported - 59% (Group B1) and 62% (Group B2) of participants **SOLICITED AEs** *Common* Local Reactions - Solicited local reactions were more frequent in the 1±5 years' age stratum [Groups A1 (76%) and Group B1 (68%)] of children than in the other age strata (31%±41% of individuals receiving the 4-site/1-week ID regimen and 33%± 41% of individuals receiving the 2-site/TRC ID regimen) - Most frequently reported solicited local AEs were injection site: → Tenderness in the 1±5 years' age stratum (ranging from 7% to 21% of children across study groups → Injection site pain in the 6±17 years' age stratum (in 4±14% of participants in all groups), and → Injection site erythema in the ≥18 years' age stratum (ranging from 1% to 16% of adults across study groups). Systemic Reactions - Solicited systemic AEs were reported in 33%±42% of participants receiving the 4-site/ 1-week ID regimen and 33%±46% of participants receiving the 2-site/TRC ID regimen and were more frequently reported in the ≥18	

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							years age stratum - Most frequent solicited systemic AEs in the 1±5 years age stratum were: ➢ Fever (reported in 7% of children in Group A1 and 17% in Group B1) and ➢ Sleepiness (14% in children Groups A1 and B113% of children in group B1 - Most frequent solicited systemic AEs in 6±17 years age stratum were: ➢ Headache (in 13% of participants in Group A1 and 16% in Group B1) and ➢ Fatigue (for 12% of participants in Group A1 and 11% in Group B1 - Most frequent solicited systemic AEs in participants aged ≥18 years were: ➢ Headache (ranging from 19% in Group B1 to 35% in Group B2) ➢ Fatigue (ranging from 19% in Group A2 to 27% in Group B2) *Severe* - Severe solicited local and systemic AEs were reported in 0%±2% of participants in all age groups; most solicited AEs were mild to moderate in intensity. **UNSOLICITED** - Unsolicited AEs were reported in ➢ Group A1: 73% and ➢ Group A2: 84%, ➢ Group B1: 79% and ➢ Group B2: 82% - Unsolicited AEs possibly or probably related to vaccination were reported in Group A1 (66%), Group A2 (84%), Group B1 (65%) and Group B2 (80%) - Incidence of severe unsolicited AEs at least possibly or probably related to vaccination was 1% in Groups A1 and B1 and 0% in Groups A2 and B2 - Most frequently reported AEs after any vaccination were in the “general	

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							disorders" and "administration site conditions" "system organ class", followed by "infections and infestations" - Overall, the most frequent AE was injection site erythema, with incidences ranging from 37% (Group B1) to 61% (Group A2) of participants in all groups - No AEs leading to withdrawal from the study were reported. Serious AEs - SAEs were reported in 3%±6% of participants; none of them were considered related to vaccination. - All SAEs except 1 (HIV infection in an adult in Group A1) were recovered/ resolved by the end of the study - No deaths were reported during the study	

Evidence Table: Safety
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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
13. Angsuwatcharakon P, Khomvilai S, Limsuwan K, Ratananpinit N, Khamcat A, Sanitnai T & Tantawichen. Immunogenicity and Safety of WHO-approved TRC ID Regimen with a Chromatographically Purified Vero Cell Rabies Vaccine with or Without Rabies Immunoglobulin in Children. Expert Review of Vaccines. 2017; 19:33	Pre- and post-intervention study Obj: To assess the immunogenicity of chromatographically purified Vero cells Rabies Vaccine (CPRC) when administered ID for PEP in paediatric patients Methods:		39 subjects Non-immunized patients aged less than 15 years Who had possible rabies exposure and classified as WHO categories II or III Recruited at outpatient rabies immunization clinic of Queen Saovabha Memorial Institute, Thai Red Cross Society	ID rabies vaccine 2-site ID Thai Red Cross Regimen (TRC-ID; 2-2-2-0-2-0) using two 0.1mLID doses of CPRV with or without RIG for children in Thailand	-	1 year (30 minutes 3 days after vaccination for adverse reactions)	**RESULTS** Adverse Events - Most of the patients experienced local adverse reactions at the site of intradermal injection, such as local erythema (66.7%), induration (46.8%), pain (25.0%), and itching (26.9%), but these were self-limiting within 2 days and required no treatment - After rabies vaccination, myalgia was reported by 12.8% of patients, and 5.1% of patients had fevers - At one year after vaccination, adequate follow-up was achieved in 76.9% of the cases, and all patients were alive and healthy. There - No serious systemic adverse reactions were observed in any of the patients after vaccination.	