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Rabies Pre-Exposure Prophylaxis: A Systematic Review on Safety, Immunogenicity and Booster Recommendations

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Abstract

Rabies infection is a serious and fatal disease that disproportionately affects children and low socioeconomic groups. Pre-exposure prophylaxis (PrEP) is a preventive strategy to protect high-risk groups. Timely updating recommendations for rabies PrEP are needed, especially to meet the needs of the underserved population. This review aimed to find recent evidence available to evaluate the safety and immunogenicity of rabies PrEP of reduced dose and duration; intramuscular (IM) and intradermal (IM) administration; and to assess booster recommendations following rabies PrEP. The literature review was conducted according to PRISMA guidelines for systematic reviews and meta-analyses. A literature search of PubMed, Google Scholar and Scopus was performed from the database for studies in the past five years (1st Jan 2017-30th May 2021). Of 45 studies identified, 15 publications met the inclusion criteria for safety, dosage, immunogenicity and booster recommendations. Most studies identified that the recommended dose and duration is safe and immunogenic for children and adults. Rabies vaccine booster is indicated for occupational exposure. The current recommendation on rabies PrEP is safe for adults and children, and the immunogenicity is not inferior to the 1-dose 3-visit regime, with equivalent effectiveness via both routes (ID and IM).

Keywords: Rabies, Pre-exposure prophylaxis, Safety, Immunogenicity.

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Introduction

Rabies is an infectious disease caused by rabies virus which is responsible for approximately 59,000 deaths in over 150 countries, mainly in Asia and Africa (Taylor & Nel, 2015). The disease disproportionately affects children below 15 years old, especially among poor communities in rural areas. However, most of these cases are underestimated, as the affected regions often underreported deaths (*Rabies*, n.d.). The disease is highly fatal once the infected person develops neurological symptoms due to rabies encephalitis (Jackson, 2016). The death from rabies infection could be preventable through various strategies, such as prevention at the reservoir through canine vaccination or by administration of rabies vaccines as well as rabies immunoglobulin following rabies virus exposure, either through bites, scratches, or licking from suspected rabid animals (World Health Organization (WHO), 2014).

Pre-exposure prophylaxis (PrEP) is another preventive strategy involving giving a course of rabies vaccine either through the intramuscular or intradermal route. Administration of PrEP could protect from rabies infection as the vaccine enables fast recall of memory immune responses once the person re-exposes to the virus. PrEP-protected individuals may only require fewer doses of post-exposure prophylaxis and may not require rabies immunoglobulin, which is expensive and largely inaccessible in many parts of the world. Prevention through PrEP could provide benefit for those at high risk of rabies virus exposure, particularly among occupational exposure to rabies virus (e.g., veterinary staff and laboratory worker that is regularly handling specimens with Lyssavirus), among the population that is living in an endemic area with high dog bite incidence (more than 5% per year), or among traveller that planned to visit remote areas that is endemic with the disease where the post-exposure prophylaxis medication is inaccessible (World Health Organization, 2018a).

In 2018, the World Health Organization (WHO) updated their recommendations regarding PrEP, especially the dosage, regimens, and the number of visits to get PrEP vaccination (World Health Organization, 2018a). In 2018 WHO recommendations, the dosage of intramuscular vaccine is a one-site injection, either 0.5mL or 1.0mL, depending on the volume of each vial. The regimen has been reduced from three visits on day 0, day 7, and day 21 or day 28 (in 2014 recommendations) to only two visits on day 0 and day 7. Reduction of visits can help to enhance compliance and, at the same time, achieve adequate protection as effective as three doses of vaccine. Meanwhile, the same position paper has maintained its recommendations on six monthly rabies antibody serological monitoring for high occupational risk. WHO also recommended administering booster doses if the titer falls below 0.5 IU/mL with a one-site intradermal or one-site intramuscular booster vaccine. Hence, to meet the need of a high-risk population, more evidence is needed to achieve better outcomes but shorter, less costly, and more feasible PrEP protocols without compromising their safety & effectiveness (Safety, 2012). This review aims to evaluate evidence on the safety and immunogenicity of rabies PrEP schedule for intramuscular and intradermal administration, the reduced dose and duration, and the rabies vaccine booster recommendations.

Methods

The literature review was intended to update the evidence on pre-exposure prophylaxis following the 2018 WHO rabies vaccine position paper. The literature review was conducted according to PRISMA guidelines for systematic reviews and meta-analyses (Page et al., 2021). Two web-based search engines and one database were used in the literature search. PubMed, Google Scholar and Scopus databases were searched to identify relevant studies, and only studies in the past five years were included (1st Jan 2017-30th May 2021). The only

original article included for review while unpublished manuscripts, letters to the editor, systematic reviews, articles not measuring the outcome of interest, articles involving animal studies, non-English articles and conference abstracts were excluded. The literature review was done by including both open access and non-open access articles. The last search was conducted on 30th May 2021.

The search strategy was already used in another study before (Kessels et al., 2017). The search string used was: "rabies" AND "pre-exposure" AND ("prophylaxis" OR "vaccin*"). Filters applied, including 'search in the title or abstract only' and 'last 5 years.' The selection and data collection process were done in two phases in which the first phase was screening by reading the title and abstract. The second phase was done by reading the full text. All of the processes were done by the reviewer independently. Since there were three reviewers, an agreement was achieved by choosing the option with two votes.

Data synthesis was done with selected articles' characteristics were first compiled in a spreadsheet and characterized by general information such as citation reference, publication year, study location, type of study, study design and type of vaccine used. Spreadsheets were uploaded in Google drive, which makes them transparent for all reviewers. Data were then extracted from respective articles according to the three objectives of this systematic review in different spreadsheets. All extracted data in different spreadsheets was analyzed and discussed before a final consensus was gained among reviewers.

Results

The literature search yielded 45 published articles, of which 28 publications remained after the removal of duplicates. These publications were screened for eligibility, and 13 were excluded. Fifteen publications met the inclusion criteria for safety, dosage, immunogenicity and booster recommendations (Table 1). The PRISMA flowchart shows identified articles' selection and screening (Figure 1).

Table 1: Summary of the included publications

Reference	Publication type/ year	Study design	Study location	Prophylaxis	Vaccines
Janewongwirot, P. (Janewongwirot et al., 2019)	Journal article/ 2019	Randomized control trial	Thailand	PVRV	Children
Recuenco, S. (Recuenco et al., 2017)	Journal article/ 2017	Randomized control trial	Atlanta	PCECV	Adults
Soentjens, P. (Soentjens, De	Journal article/ 2019	Randomized control trial	Belgium	PCEV	Adults

Koninck, et al., 2019)					
Damanet, B. (Damanet, Costescu Strachinaru, et al., 2020; Damanet, Strachinaru, et al., 2020)	Journal article/ 2020	Retrospective study	Belgium	PCECV, vaccination against yellow fever, tetanus, diphtheria, pertussis and meningococcal group A, C, W and Y	Adults
Angsuwatcharakon, P. (Angsuwatcharakon et al., 2020)	Journal article/ 2020	Randomized control trial	Thailand	PVRV, JE-CV	Children
Furuya-Kanamori, L. (Furuya-Kanamori et al., 2021)	Journal article/ 2021	Retrospective study	Australia	HDCV (MIRV), PCECV, PVRV	Adults
De Pijper, C. A. (Cornelis A De Pijper et al., 2021)	Journal article/ 2021	Prospective study	Amsterdam	PCECV	Adults
Soentjens, P. (Soentjens, Andries, et al., 2019)	Journal article/ 2019	Randomized control trial	Belgium	HDCV (MIRV)	Adults
De Pijper, C. A. (Cornelis	Journal	Prospective	Netherlands	PVRV	Adults

Adrianus De Pijper et al., 2018)	article/ 2018	study			
Huttner, A. (Huttner et al., 2021)	Journal article/ 2021	Retrospective study	Switzerland	PCECV/HDCV (MIRV) if short supply of PCECV	Adults
Hardanahalli S., R. (Hardanahalli S et al., 2017)	Journal article/ 2017	Prospective study	India	PCECV	Children, adults
Parize, P. (Parize et al., 2021)	Journal article/ 2021	Retrospective study	France	PVRV, PCECV	Adults
Van Nieuwenhove, M. D. M. (Van Nieuwenhove et al., 2019)	Journal article/ 2019	Retrospective study	Belgium	PCECV	Adults
T. P. Endy et al. (Endy et al., 2020)	Journal article/ 2020	Randomized control trial	USA	PCECV	Adults

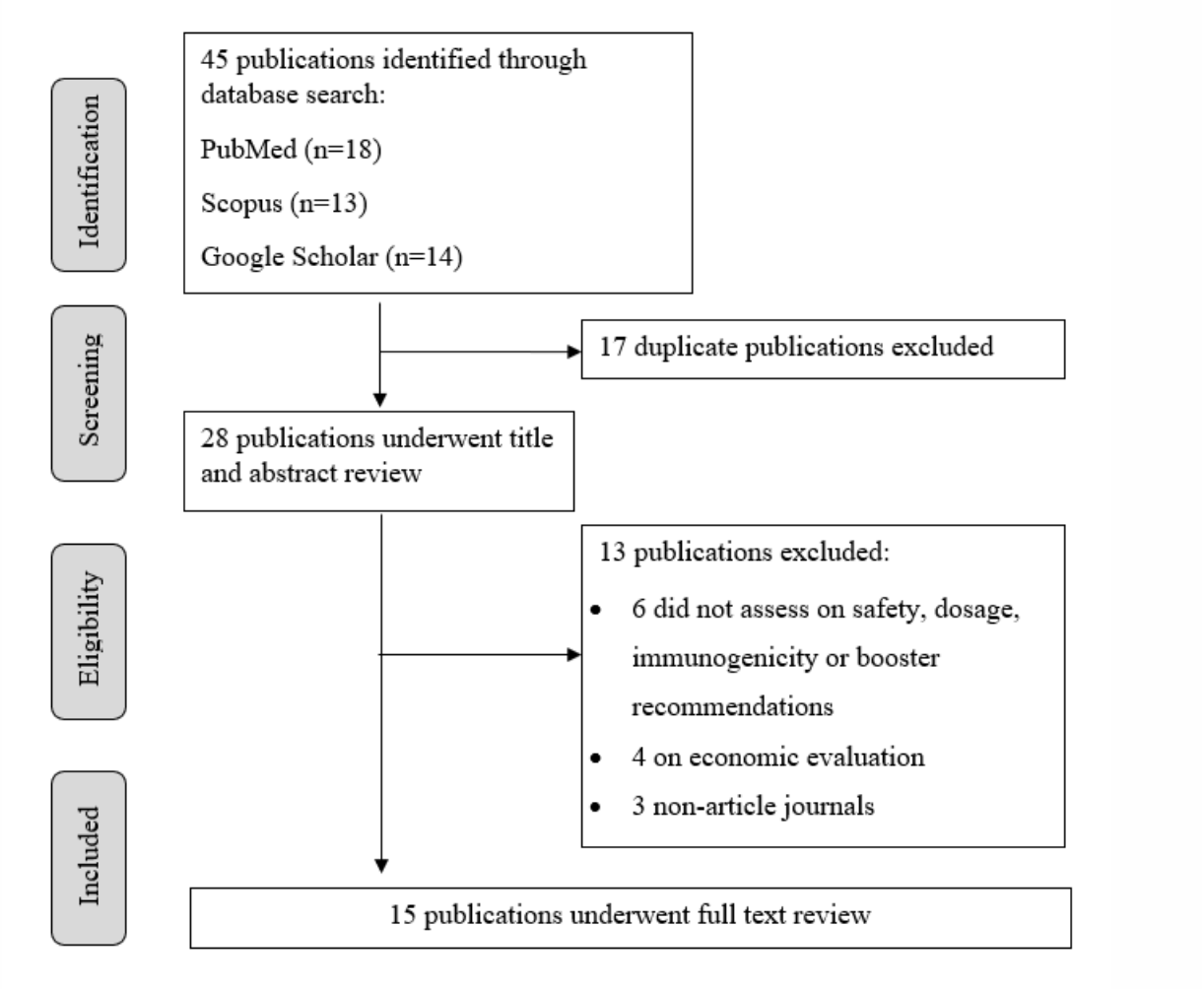

Figure 1: The PRISMA flowchart of identified articles' selection and screening

Safety

The study search identified seven studies evaluating the safety of rabies vaccination prophylaxis with or without immunogenicity (Angsuwatcharakon et al., 2020; Endy et al., 2020; Hardanahalli S et al., 2017; Huttner et al., 2021; Recuenco et al., 2017; Soentjens, Andries, et al., 2019; Soentjens, De Koninck, et al., 2019). Among them, three studies included the safety evaluation using the latest regimes recommended by the World Health Organization (WHO) (Angsuwatcharakon et al., 2020; Endy et al., 2020; O'Brien & Nolan, 2019; Soentjens, Andries, et al., 2019). In total, five studies were conducted after WHO had updated its recommendations in 2018 (Angsuwatcharakon et al., 2020; Endy et al., 2020; Huttner et al., 2021; Soentjens, Andries, et al., 2019; Soentjens, De Koninck, et al., 2019). However, another two studies were conducted before 2018 (Hardanahalli S et al., 2017; Recuenco et al., 2017). The latter were included because their results were still relevant to our study (Hardanahalli S et al., 2017; Recuenco et al., 2017). Most studies found that the dose and duration were safe and immunogenic to adults (Angsuwatcharakon et al., 2020; Endy et al., 2020; Soentjens, Andries, et al., 2019; Soentjens, De Koninck, et al., 2019) and children (Angsuwatcharakon et al., 2020; Hardanahalli S et al., 2017).

The current vaccination prophylaxis regime was safe for adults (Angsuwatcharakon et al., 2020; Endy et al., 2020; Soentjens, Andries, et al., 2019). Mild and transient local

irritation at the injection site were the common effects that occurred after primary injection (43.4%) as compared to 0.1ml one intradermal dose in a 3-visit regime (p-value 0.07) (Soentjens, Andries, et al., 2019). Nevertheless, three participants in the study experienced severe adverse effects, one from a 3-visit regime following primary injection and another two from the current schedule following booster dose. These two participants had esophagitis, dyspnea, angioedema and urticaria (Soentjens, Andries, et al., 2019). Table 2 summarises the adverse events experienced by the study participants.

Two studies among children identified that the vaccine was safe for children (Angsuwatcharakon et al., 2020; Hardanahalli S et al., 2017). A group of 150 children from a poor urban locality aged 5 to 10 years were selected in a study (Hardanahalli S et al., 2017), and 49 children aged 12 to 16 months were enrolled in another study (Angsuwatcharakon et al., 2020). Some children only developed local adverse reactions such as pain, redness, pruritus and itching, and some had fever and headache. No severe adverse reactions were recorded (Angsuwatcharakon et al., 2020; Hardanahalli S et al., 2017).

A study in Switzerland was done on Multiple Sclerosis (MS). Only 10.9% of their patients had relapsed after a year post rabies vaccination. Some patients even received up to seven repeated doses of the rabies vaccine, and the authors did not find any relation to MS relapse (Huttner et al., 2021).

Furthermore, a study in Thailand administered the rabies vaccine simultaneously with the Japanese encephalitis (JE) vaccine on day 0 to their healthy children. No immediate or severe adverse vaccine reactions were identified (Angsuwatcharakon et al., 2020).

Table 2: Adverse events recorded

Reference	Route/ Regime/ Vaccine type	Adverse events	No. (%) of cases	Remarks
Recuenco, S. (Recuenco et al., 2017)	1ID/ 1IM/ day 0, 7, 21/ PCECV	No severe adverse events (Erythema, induration, tenderness, headache, fatigue, fever, insomnia)	-	-
Soentjens, P. (Soentjens, De Koninck, et al., 2019)	2ID/ day 0/ PCEV	No severe adverse events. Mostly has local irritation (redness, swelling, rash, itching)	14.9%	-
Angsuwatcharakon, P. (Angsuwatcharakon et al., 2020)	2ID/ day 0, 28/ PVRV	No severe adverse events	-	-
	1ID/ day 0, 7, 28/ PVRV		-	-
Soentjens, P. (Soentjens, Andries, et al., 2019)	3ID/ day 0, 7 28/ HDCV	Reversible diplopia and hemianopsia	1	14 days after final rabies vaccination and some days after receiving MMR vaccines in other centers (violating protocol)

	2ID/ day 0, 7/ HDCV	Esophagitis	1	After booster dose
		Dyspnea, angioedema, urticaria	1	
Huttner, A. (Huttner et al., 2021)	Not stated	Not associated with Multiple Sclerosis (MS) relapses	-	A study among MS patients
Hardanahalli S., R. (Hardanahalli S et al., 2017)	3ID/ day 0, 7, 21/ PCECV	Mild reactions and subsided without any complication (Local reactions: pain, redness, itching. Systemic reactions: fever, myalgia, fatigue, headache)	5.1% (children)	-
			5.0% (rag pickers)	-
			10.4% (veterinary students)	-
T. P. Endy et al. (Endy et al., 2020)	3IM/3ID/ day 0, 7, 21 or 28/ PCECV	More adverse events in ID groups compared to IM groups (pain, itching, swelling, fatigue, low-grade fever,	66.7% (IM group) 91.7% (ID group)	-

	2IM/2ID/ day 0, 7/ PCECV	muscle aches)	66.7% (IM group) 90.9% (ID group)	-

Immunogenicity

New Regime

With the new dose and route recommended by WHO (O'Brien & Nolan, 2019), the adequate antibody level was reached in more than 86% of the participants (Angsuwatcharakon et al., 2020; Endy et al., 2020; Furuya-Kanamori et al., 2021; Soentjens, Andries, et al., 2019). Rabies serum antibody concentration of 0.5 IU/ml or more indicated an adequate serum conversion. It can be achieved after 14 days post-primary vaccine and day 7 post-booster (Angsuwatcharakon et al., 2020; Endy et al., 2020; Soentjens, Andries, et al., 2019; World Health Organization, 2018b).

Australia

From 2000 until 2016, travellers who attended a specialized travel medicine clinic in Adelaide were given the ID rabies vaccine according to three different schedules (Table 3). The choice was based on the clinician, cost, time and ability of the patient to return to the clinic for the subsequent doses. As overall, 92.5% of all travellers achieved adequate rabies antibody levels. Among them, 93.4% of the patients who received a single dose for three visits had adequate rabies antibody levels, compared to two-dose for two visits (86.2%) and four-dose for a single visit (76.2%) schedules. Younger travellers aged less than 30 also had more adequate antibody levels than those aged 30 and above. However, the antibody level depends on the timing of the test, in which the reading was the lowest if it was done less than 14 days post-primary vaccine, and the reading peaked if it was done between 14 to 34 days post-primary vaccine (Furuya-Kanamori et al., 2021).

Different routes of administration

Two studies were identified comparing immunogenicity differences among the intramuscular and intradermal routes. In these studies, all participants had adequate rabies antibody levels post-primary vaccine, regardless of the route (Angsuwatcharakon et al., 2020; Recuenco et al., 2017). The geometric mean titer (GMT) for both routes among adults peaked at 14 days post-primary vaccine and maintained its titer of more than 0.5 IU/ml up until 160 days (Recuenco et al., 2017). The titer among children remained above the threshold level for up to a year (Angsuwatcharakon et al., 2020). There was no difference in the GMT values between both routes in both studies (Angsuwatcharakon et al., 2020; Recuenco et al., 2017).

Different Dose and Duration

Three studies were identified evaluating the vaccine schedules with different doses and durations (Damanet, Strachinaru, et al., 2020; Janewongwirot et al., 2019; Van Nieuwenhove et al., 2019). In a study among healthy children of 2 to 12 years old in Thailand comparing two-visit and three-visit regimes, all had rabies virus antibody titer of 0.5 IU/ml or more at day 14 post-primary vaccination. Notably, 100% of those in the three-visit regime were able to maintain the titer at one year compared to only 80% of those in the two-visit regime. The remaining 20% of the children were from the two-visit regime with titers of less than 0.5 IU/ml at one-year post-primary vaccine, predominantly males and children aged more than six years (Janewongwirot et al., 2019). Another two studies were conducted among the armies. Both provided a single-dose 3-visit intradermal rabies vaccine to the participants. However, the variability occurred when some participants received the dose earlier than scheduled, at the correct timing, late and very late than scheduled. Regardless of the variability, 99.9% to 100% of the participants' rabies virus antibodies developed an antibody level of 0.5 IU/ml (Damanet, Strachinaru, et al., 2020; Van Nieuwenhove et al., 2019). The antibody level was

significantly influenced by the timing of the test, in which the level was higher in 7 to 28 days post-primary vaccination as compared to those later than 28 days (p = 0.047) (Van Nieuwenhove et al., 2019). Being female, age younger than 30 years, and the normal timing of the serology (7 to 28 days post-primary vaccination) significantly influenced the antibody titer level to be 3 IU/ml or more (Damanet, Strachinaru, et al., 2020).

Booster

There were six studies evaluating the effect of boosters on immunogenicity. All of them demonstrated that adequate rabies antibody titer could be achieved from 98.7% up to 100% of participants (Cornelis A De Pijper et al., 2021; Furuya-Kanamori et al., 2021; Janewongwirot et al., 2019; Parize et al., 2021; Soentjens, Andries, et al., 2019; Soentjens, De Koninck, et al., 2019) regardless of the timing of booster, a booster dose (Soentjens, De Koninck, et al., 2019) or vaccine schedules (Cornelis A De Pijper et al., 2021; Parize et al., 2021; Soentjens, Andries, et al., 2019). P. Janewongwirot et al.'s study revealed that the rabies antibody titers were above the threshold level in all of the children. The titers increased from 0.8 IU/ml pre-booster to 20.9 IU/ml 7-day post-booster in the 2-visit regime and from 1.7 IU/ml pre-booster to 22.2 IU/ml 7-day post-booster in 3-visit regime (Janewongwirot et al., 2019). Participants with a 4-dose ID booster have significantly higher rabies antibody titer than a 2-dose ID booster (p = 0.0228) (Soentjens, De Koninck, et al., 2019).

Meanwhile, participants who received the current recommended vaccine regime by WHO had significantly higher antibody titer after the booster dose as compared to the previous regime (p < 0.001) (Soentjens, Andries, et al., 2019). Nevertheless, both regimes had a titer of more than 0.5 IU/ml (Soentjens, Andries, et al., 2019; Soentjens, De Koninck, et al., 2019). Some participants maintained adequate titers more than five years after a single booster dose (Parize et al., 2021). Only two cases were observed to have severe adverse reactions after booster dose (Table 3) (Soentjens, Andries, et al., 2019). In contrast, others only had local irritation at the injection site, such as redness, swelling, rash and itching (Soentjens, Andries, et al., 2019; Soentjens, De Koninck, et al., 2019).

Table 3: Pre-exposure rabies prophylaxis

Reference	Year	Schedule	Route	Booster	Sample specification	Serology result	Safety
Janewongwirot, P. et al. (Janewongwirot et al., 2019)	2019	1. Single-dose 2-visit (day 0, 28) 2. Single-dose 3-visit (day 0, 7, 28)	0.5ml IM	0.5ml IM (day 365)	Healthy children aged 2-12 years with. No history of rabies vaccination. Randomized to receive vaccine 2-doses or 3-doses group	1. Day 14: 100% of participants from both groups had RVNA titers ≥ 0.5 IU/ ml after primary vaccination. 2. Day 365 (pre-booster): 2-doses group had 80% with RVNA titers ≥ 0.5 IU/ ml (GMT RVNA 0.8IU/ml). 3-doses group had 100% with RVNA titers ≥ 0.5 IU/ ml (GMT RVNA 1.7 IU/ml) (p=0.01) 3. Post-booster: Both groups had 100% RVNA titers ≥ 0.5IU/ml. The 2-doses group had GMT RVNA 20.9 IU/ml. The 3-	N/A

						doses group had GMT RVNA 22.2 IU/ml.	
Recuenco, S. (Recuenco et al., 2017)	2017	1. PrEP group: single dose day 0,7,21 (ID route) 2. PrEP group: single dose day 0,7,21 (IM route) 3. Booster group: a person with previous PrEP was given booster day 0 (ID route) 4. Booster group: a person with previous PrEP was given booster day 0 (IM route)	0.1ml ID or 1.0ml IM	N/A	CDC staff age 18 years and above.	1. RVNA titers day 14-21 increased at a similar rate for both ID and IM groups in the PrEP regime. 2. All group participants had RVNA titers > 0.5IU/ml after 14 days of complete vaccination.	No serious adverse reaction. Common reactions were erythema, induration and tenderness at the injection site.
Soentjens, P. (Soentjens, De Koninck, et al., 2019)	2019	0.1ml 2-dose single visit day 0	ID	After 1 year PrEP regime: 1. Booster single visit 4-	Belgian Armed Forces age 18-54 years	1. Day 7 post-booster: 99.3% participants in both booster groups had	No serious adverse event. Only 14.9% had mild to transient local

				dose 0.1ml 2. Booster single visit 2-dose 0.1ml		antibody titers > 0.5IU/ml 2. Day 7 post-booster: Significant higher GMT after 4-dose booster (20IU/ml) compared to 2-dose booster (14IU/ml) (p=0.0228)	irritation after PrEP. Post-booster local irritation was seen higher in the 4-dose booster regime compared to the 2-dose booster regime (53% vs 49.6%).
Damanet, B. (Damanet, Costescu Strachinaru, et al., 2020)	2020	0.1ml 2-dose 2-visit 1. Early (day 0, ≤6) 2. Correct (day 0,7) 3. Late (day 0, 8-56)	ID	N/A	Belgium Armed Forces who had never received any vaccination before study	1. 98.7% had RVNA ≥0.5IU/ml 2. 39.5% had a "very good protection against rabies" (RVNA > 10 IU/mL) 3. 4 subjects (1.3%) had RVNA < 0.5 IU/mL 4. There is a significantly higher RVNA in 'late" second dose administration than correct the second dose on day 7.	N/A
Damanet, B.	2020	Single-dose 3-	ID	N/A	Belgium Armed	1. All participants	N/A

(Damanet, Strachinaru, et al., 2020)		visit 0.1ml 1. Early (day 0, ≤6, ≤20) 2. Correct (day 0, 7,21-28) 3. Late-variable (day 0, 8-35, 29-56) 4. Late- vary variable (day 0, >35, >56)			Forces	seroconverted with RVNA ≥0.5 IU/ml. 2. Better immune response in participants aged less than 30 years compared to other age groups. 3. Female is a predictor for RVNA ≥ 3IU/ml. 4. Very late vaccination schedule is a predictor to RVNA >10IU/ml compared to "correct" schedule	
Angsuwatcharakon, P. (Angsuwatcharakon et al., 2020)	2020	PrEP: 1. Group A: 0.1ml ID 2-dose 2-visit (day 0, 28) + JE-CV (day 0, 365) 2. Group B: 0.5ml IM 1-dose 3-visit (day 0,	ID, IM	N/A	Healthy children age 12-16 months.	1. Day 42 post vaccination: All children had RVNA > 0.5IU/ml. 2. Day 365 post vaccination: 92.3% children in Group A and 92.3% children in Group B had RVNA	No vaccine-related severe adverse effect observed. Common local reaction: Group A had erythema and pruritus at the site of injection.

		7, 28) + JE-CV (day 0, 365)				>0.5IU/ml.	Group B had pain at the injection site.
Furuya-Kanamori, L. (Furuya-Kanamori et al., 2021)	2021	PrEP: 1. 0.1ml 1-dose 3-visit (day 0, 7, 21-28) 2. 0.1ml 2-dose 2-visit (day 0, 7) 3. 0.1ml 4-dose 1-visit (day 0)	ID	Some had ID boosters after 12 months of primary vaccination	Travellers	Serology tested either (1) after primary ID PrEP or (2) after a booster. 1. 92.5% of travellers had antibody titer ≥0.5IU/ml. Group 1 PrEP had the highest proportion of antibody titer ≥0.5IU/ml compared to other groups. Aged 50 years and above had 89.4% antibody titer ≥0.5IU/ml. 2. 98.7% of travellers had antibody titer ≥0.5IU/ml. Aged 50 years and above had 97.9% antibody titer ≥0.5IU/ml. That booster, for more than 3 years,	N/A

						had all antibody titer ≥0.5IU/ml.	
De Pijper, C. A. (Cornelis A De Pijper et al., 2021)	2021	PrEP at least 10 years before study 1. 3-dose IM 2. 3-dose ID 3. Divergent (2 or 3 dose regime)	IM	1ml IM	Healthy volunteers aged 18 years and older	1. All participants had antibody titer ≥0.5IU/ml after a 1-week booster.	N/A
Soentjens, P. (Soentjens, Andries, et al., 2019)	2019	PrEP: 1. Control group: 0.1ml 1-dose 3-visit (day 0, 7, 28) 2. Intervention group: 0.1ml 2-dose 2-visit (day 0, 7)	ID	0.1ml ID booster 1-3 years after primary vaccination	Belgian Armed Forces	1. Day 7 post-booster: 100% participants had RFFIT >0.5IU/ml. 2. Day 7 post booster: 96% in the intervention group had antibody titer >10IU/ml compared to the control group (83%). 3. GMT was higher in the control group after primary vaccination. But GMT was higher in the intervention	1. One case had a severe adverse event (reversible diplopia and hemianopsia) 14 days after the last dose of the primary vaccine (control group). 2. One case had esophagitis after booster (intervention group). 3. One case with dyspnea, angioedema, and urticaria after booster (intervention group).

						group after the booster.	4. Local irritation occurred more frequently in the control group after primary vaccination. 5. Local irritation occurred more frequently in the intervention group after the booster dose.
De Pijper, C. A. (Cornelis Adrianus De Pijper et al., 2018)	2018	0.1ml (day 0, 7, 21-28)	ID	N/A	Military personnel	1. 99.3% had antibody titer > 0.5IU/ml after 2 doses (GMT 7.59 IU/ml) 2. Another 3 participants seroconverted after third dose.	N/A
Huttner, A. (Huttner et al., 2021)	2021	At least one dose PrEP	N/A	N/A	Multiple Sclerosis patients. They were receiving disease-modifying therapy during the study period. 91% received at least one other vaccine during the study period.	N/A	The annualized relapse rates in the pre-exposure risk, exposure-risk, and post-risk periods were 0.44, 0.22, and 0.10, respectively (the rate ratio for exposure-risk to pre-exposure periods was 0.509)

Hardanahalli S., R. (Hardanahalli S et al., 2017)	2017	PrEP: 0.1ml 1-dose 3-visit (day 0, 7, 21)	ID	N/A	Group 1: Children from an urban poor locality Group 2: Rag-pickers Group 3: Government Veterinary college students	N/A	Overall adverse drug reactions: 5.1% in children. 5.0% in rag-pickers. 10.4% in veterinary students. Common local reactions were pain, redness and itchy at the injection site. Systemic ADRs were fever, myalgia, headache and fatigue.
Parize, P. (Parize et al., 2021)	2021	Had received PrEP regime before study period (1-dose IM, 3-visit)	IM	Had received a booster dose before the study period	Laboratory workers of the Institut Pasteur of Paris	1. 17.2% of participants had inadequate antibody titer after primary vaccination (without booster) 2. 0.5% had an inadequate response after booster 3. Significant	N/A

						factors for inadequate antibody titer were male, more than 6 months intervals between primary vaccine and serology test, and simultaneous administration with non-rabies vaccine during PrEP	
Van Nieuwenhove, M. D. M. (Van Nieuwenhove et al., 2019)	2019	0.1ml 1-dose 3-visit schedules: 1. Early (day 0, ≤6, ≤ 20) 2. Correct (day 0, 7, 21-28) 3. Late-variable (day 0, 8-35, 29-56) 4. Late- very variable (day 0, >35, >56)	ID	N/A	Belgian Armed Forces	1. 99.9% developed RVNA ≥0.5IU/ml. 2. A higher proportion of RVNA >10IU/ml in a very late variable group compared to the correct group (p=0.047) 3. Normal timing for serology determination had a significantly higher frequency of RVNA > 10IU/ml than later-than-	N/A

						planned.	
T. P. Endy et al. (Endy et al., 2020)	2020	PrEP: Group 1: 1ml IM 3-visit (day 0, 7, 21 or 28) Group 2: 0.1ml ID 3-visit (day 0, 7, 21 or 28) Group 3: 1ml IM 2-visit (day 0, 7) Group 4:0.1ml ID 2-visit (day 0, 7)	IM, ID	1ml IM at 1 year after first dose	Adults aged 18-60 years at the State University of New York Upstate Medical University (SUNY-UMU) in Syracuse, New York	1. All participants in groups 1-4 achieved >0.5IU/ml rabies antibody titer by day 14 and 28 posts primary vaccine and on day 372 after the booster. 2. At day 365, only 64% in group 1, 45% in group 2, 58% in group 3 and 60% in group 4 had rabies antibody titer > 0.5IU/ml, with p-value of 0.39, 0.79 and 0.86 respectively as compared to group 1.	1. Common adverse events at the injection site: pain, itch, swelling. 2. Common systemic adverse events: fatigue, low-grade fever, muscle ache. 3. Those who received ID vaccines experienced more local (91.7%) and systemic (90.9%) adverse events compared to those who received IM vaccine (66.7% and 66.7% for local and systemic adverse events, respectively.

Discussion

The conventional rabies vaccine previously recommended by WHO had been practised differently (O'Brien & Nolan, 2019). For example, in Belgium, their military personnel have received rabies PrEP before deployment since 2009. Due to their nature of work, instead of providing their armies with conventional rabies PrEP regime, the 2-dose 0.1ml ID 2-visit schedule has been practised (Damanet, Costescu Strachinaru, et al., 2020). There were also timescale variations in the rabies vaccination schedule because they could not comply with the vaccine's exact timing as they had deployed away from their centre (Damanet, Costescu Strachinaru, et al., 2020; Damanet, Strachinaru, et al., 2020), similarly to travellers from Australia. Due to tight departure timing, cost and ability of the travellers to return to the clinic, the treating clinician helped to provide a suitable rabies vaccine schedule, which can be different from the conventional regime (Furuya-Kanamori et al., 2021). Hence, WHO has updated the regime to improve access to the rabies vaccine, especially among the high-risk populations (O'Brien & Nolan, 2019; World Health Organization, 2017a).

Studies demonstrated that rabies vaccine is safe in adults and children (Angsuwatcharakon et al., 2020; Endy et al., 2020; Hardanahalli S et al., 2017; Huttner et al., 2021; Recuenco et al., 2017; Soentjens, Andries, et al., 2019; Soentjens, De Koninck, et al., 2019). The current recommended dose, route and duration of primary rabies vaccine is immunogenic and comparable with the conventional dose, route and duration (Angsuwatcharakon et al., 2020; Damanet, Strachinaru, et al., 2020; Cornelis Adrianus De Pijper et al., 2018; Endy et al., 2020; Furuya-Kanamori et al., 2021; Janewongwirot et al., 2019; Parize et al., 2021; Recuenco et al., 2017; Soentjens, Andries, et al., 2019; Van Nieuwenhove et al., 2019). Additionally, it can be safely administered simultaneously with the JE vaccine in children (Angsuwatcharakon et al., 2020). It is also safe to give MS patients as it does not associate with MS relapse (Huttner et al., 2021).

The circulating rabies virus antibody was detectable even after 9 years post-primary vaccination; up to 80% of participants received the vaccine through the IM route. No booster dose was given in that study (World Health Organization, 2017b, 2018b). Rabies vaccine booster dose after PrEP also confers higher and long-term immune response. Seropositivity can be detected as early as 7 days post-booster dose up to more than 5 years (Cornelis A De Pijper et al., 2021; Endy et al., 2020; Furuya-Kanamori et al., 2021; Parize et al., 2021; Soentjens, Andries, et al., 2019; Soentjens, De Koninck, et al., 2019). Current WHO recommendation indicated that no further PrEP booster doses are needed after primary vaccination for individuals living in and travellers going to high-risk areas (World Health Organization, 2018b). Individual assessment is needed in which booster dose can be considered in frequent travellers that have the potential of direct contact in an extended period in remote settings where rabies is enzootic. (World Health Organization, 2017a). In occupational exposure, professionals continuously exposed to the risk will be required to have regular serology monitoring. A booster dose will be provided if the antibody falls below 0.5 IU/ml (World Health Organization, 2017a, 2018b).

Hence, in general, PrEP with or without booster is recommended to individuals with occupational exposure, such as individuals involved with rabies research and exposed to rabies biological products, animal disease control, wildlife management, involved in dog vaccination campaigns, military and religious individuals that work or reside in remote areas

(World Health Organization, 2017a). Frequent travellers to endemic rabies areas will be evaluated for eligibility for receiving PrEP (World Health Organization, 2017a, 2018b). Providing PrEP at the population level will not be cost-effective. Hence, in extreme circumstances where the rabies exposure is more than six per cent, and rabies immunoglobulin will be difficult to access, PrEP is recommended after being assessed by individual country (World Health Organization, 2017a).

Even though some studies mentioned that the conventional regime using the 3-visit schedule has a higher proportion of participants with higher rabies antibody level and persist at least up to a year as compared to the new recommended regime using a 2-visit schedule (Angsuwatcharakon et al., 2020; Furuya-Kanamori et al., 2021; Janewongwirot et al., 2019; Soentjens, Andries, et al., 2019), even a single visit of PrEP can result with adequate seroconversion (World Health Organization, 2018b). This information is useful for adapting high-risk occupations to easily comply with the new rabies vaccine schedule, such as those in the military (Soentjens, Andries, et al., 2019). Furthermore, administering the rabies vaccine through ID does not mean it is inferior to the IM administration. Evidence has shown that its immunogenicity and effectiveness can be equivalent (Denis et al., 2019; O'Brien & Nolan, 2019).

This review provides the latest evidence on rabies pre-exposure prophylaxis' safety, immunogenicity and booster, which could help policy decision-makers to protect vulnerable populations from rabies mortality.

This review is not without limitations. Our study only included published articles in English, excluding local reports in other languages and the grey literature. The strength of this review is most of the articles have study designs that are RCTs and cohort studies which provide good quality evidence even though the risk of bias due to heterogeneity is undeniable. However, most of the included articles did not assess the safety and immunogenicity of novel PrEP schedules for special populations, such as infants, pregnant women or immunocompromised persons, such as people infected with HIV. The use of PrEP in these subpopulations is highly relevant and was included as a priority question by the SAGE working group on rabies. Furthermore, Meta-analysis is not included in this review due to the limited number of literature that meet the inclusion criteria, which could raise the publication or reporting biases and are likely to produce an inappropriate summary.

Conclusion

The now recommended PrEP schedule by WHO provides a shorter vaccine regime that can help reduce the cost, the quantity of vaccine use and the number of visits. It is important that it still provides adequate immunogenicity and effectiveness while simultaneously maintaining user safety for children and adults at high risk.

Conflicts of Interest

No potential conflict of interest was reported by the authors(s).

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