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Immunogenicity and safety of human diploid cell vaccine (HDCV) vs. purified Vero cell vaccine (PVRV) vs. purified chick embryo cell vaccine (PCECV) used in post-exposure prophylaxis: a systematic review and meta-analysis

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ABSTRACT

This study comprehensively evaluated and compared three human rabies vaccines. Seven electronic databases were systematically searched. The Cochrane Handbook v5.1.0 was used to assess the risk of bias. A random-effects model was used to combine individual rates, and network meta-analysis was used for pairwise comparisons. Twenty-seven articles were included, with a total of 18,630 participants. The pooled incidence of the total adverse reaction to HDCV was significantly lower than that of PCECV. HDCV administration resulted in a lower incidence of local pain, fever, and weakness than purified Vero cell vaccine. HDCV caused a lower incidence of local pain and fever than PCECV. No significant difference was observed in terms of the seroconversion rate on day 7 or the rabies virus-neutralizing antibody titer on day 14. HDCV demonstrated superiority in terms of safety compared with the other two rabies vaccines, while the same was not observed in terms of immunogenicity.

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Rabies vaccines; post-exposure prophylaxis; immunogenicity; adverse reaction; meta-analysis

Introduction

Rabies remains one of the deadliest zoonotic diseases worldwide and is caused by the rabies virus, with diffuse encephalomyelitis being the main pathological characteristic. Rabid dogs are one of the main sources of infection. People of different ages are susceptible to rabies infection, with a case fatality rate approaching 100% following the appearance of clinical symptoms.[1,2] Globally, canine-transmitted rabies causes approximately 59,000 (95% confidence intervals (CI): 25–159,000) deaths each year and up to $8.6 billion (95% CI: $2.9–21.5 billion) economic losses.[3] Although there is currently no effective treatment for rabies, potential infections can be prevented using a series of clinical methods. Rabies exposure is divided into three categories according to the World Health Organization (WHO). For category II exposure and the above, in addition to thorough wound management, victims should also be vaccinated with a qualified rabies vaccine following the prescribed vaccination regimen. Rabies immune globulin (RIG) must be administered via injection to those under category III.[4] According to the vaccination site (intramuscular or intradermal) and the injection frequency, there are various vaccination regimens, including the five-site Essen regimen, four-site Zagreb regimen, and eight-site Thai Red Cross regimen. Among them, as the gold standard, the Essen regimen (intramuscular injection) has been widely applied worldwide.[5]

The first rabies vaccine was developed by Louis Pasteur in 1885 using the dried spinal cord of rabbits suffering from rabies.[6] With the continuous improvement and innovation of vaccine production technology, most rabies vaccines produced worldwide are now cell-culture vaccines, including human diploid cell vaccine (HDCV), purified Vero cell vaccine (PVRV), and purified chick embryo cell vaccine (PCECV).[7] Persistence of immunity after administration of the three rabies vaccines is satisfactory. According to the results of a recent randomized controlled trial (RCT) in China, the mean seroconversion rates are > 98% even after 10 years post the initial vaccination in both the HDCV and PVRV groups.[8] The seroconversion rate can also reach 95% one year after initial vaccination using PCECV.[9] As recommend by the WHO, the three rabies vaccines are widely used in Asia. PCECV has the lowest cost and is widely used in developing countries, especially India. Compared to HDCV, PVRV has been increasingly used in China in recent years due to higher cost of the former. Compared with HDCV, PVRV, and PCECV, rabies vaccines produced in animal cells are easier to manufacture and store; hence, they have a greater yield and are widely used in developing countries. However, HDCV is a vaccine cultured and manufactured using healthy human embryonic lung fibroblasts as a matrix. It is often used as a reference vaccine because it has no potential tumor-causing DNA residues or risk of foreign protein allergens, and is theoretically safer.[10] Hence, vaccine safety and immunogenicity may be influenced by the cell types used for their production *in vitro* because of differences in the composition of rabies vaccines produced in different cell-type cultures.

To date, there have been several studies comparing different types of rabies vaccines, but no study has compared HDCV, PVRV and PCECV simultaneously. In particular, a large

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proportion of studies were based on healthy individuals,[11–13] which cannot represent the real efficacy of vaccines in exposed populations. Therefore, we focused on post-exposure populations because post-exposure prophylaxis (PEP) is more common than pre-exposure prophylaxis (PrEP) in daily life. Data were collected from related studies, and the safety and immunogenicity of HDCV, PVRV, and PCECV were quantitatively evaluated and compared simultaneously through meta-analysis. Moreover, this study considered the adverse reaction (AR) rate as a measurable variable for safety, in addition to determination of seroconversion rates and rabies virus neutralizing antibody (RVNA) titer or concentration for immunogenicity.

Materials and methods

Search strategy

Chinese and English electronic databases were systematically searched from inception to November 30, 2021; the databases included the China National Knowledge Infrastructure, the Wanfang database, Sinomed, VIP, Web of Science, PubMed, and the Cochrane Library databases. The following search terms were used: "rabies," "vaccine," "effectiveness," "safety," "immunogenicity," "adverse reactions," "side effects," "RCT," "observational research." There were no limitations on language. To avoid selection bias caused by the reviewer as much as possible, the above retrieval process and the literature screening and subsequent full-text reading process were independently completed and cross-checked by two reviewers. If there was a disagreement, an agreed consensus was arrived at after discussion or referencing a third-party opinion.

Study selection

Studies that met the following criteria were included in the review: (1) Types of rabies vaccines: research used HDCV and/or PVRV and/or PCECV to induce immunity; (2) Subjects: the subjects had a clear history of exposure to confirmed or suspected rabid animals and no history of vaccination; (3) Vaccination regimen: all subjects were vaccinated by the five-site Essen regimen viz. vaccinated intramuscularly on days 0, 3, 7, 14, and 28 or 30; (4) Study design: randomized controlled trial, prospective observational study, or retrospective study; (5) Results: study provided the outcome data, such as AR and/or seroconversion rates. Studies were excluded if (1) the subjects were special populations, such as the people with HIV/AIDS, infants, and pregnant women; (2) they were cell or animal experiments; and (4) they primarily focus on vaccine development and production technology.

Data extraction

Two researchers independently extracted data from the literature which was included in the meta-analysis. The data extracted include first author's name, year of publication, country/region, study duration, inclusion and exclusion criteria for subjects, number of subjects, age distribution, sex ratio, vaccine type, exposure type, administration of rabies immunoglobulin (yes or no), and information related to the safety and immunogenicity of rabies vaccines. The measurement variables involving safety specifically included the incidence of total ARs and the incidence of some common local and systemic solicited ARs, including local pain, erythema, pruritus, edema, induration, headache, fever, myalgia, and weakness. Geometric mean titer or concentration (GMT or GMC) of RVNA in serum, seroconversion rates and their corresponding 95% CIs were metrics for immunogenicity.

Risk of bias assessment

Two reviewers independently assessed the risk of bias for each included article, according to the Cochrane Handbook V5.1.0. Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases are the seven domains of risk of bias. Each domain was judged as "low risk," "uncertainty," or "high risk" for each study.

Data analysis

Endnote X9 software was used for document screening and management. The extracted raw data were recorded in Excel 2016, and then it was imported into R v4.0.3 software for statistical analysis after a simple arrangement. First, a single-rate meta-analysis was conducted to evaluate the pooled total AR rates and seroconversion rates of HDCV, PVRV, and PCECV. Then, when we performed multiple comparisons among the three rabies vaccines, the method of adjusted indirect comparison was adopted, which is also known as network meta-analysis (NMA). The single-rate meta-analysis was conducted based on the "meta" package in R software. NMA was performed based on the Bayesian framework and was implemented by calling OpenBUGS v3.2.2 software through the "R2OpenBUGS" package in the R software. Relative risk (RR) was calculated for qualitative data, and the weighted mean difference (WMD) was calculated for quantitative data as the effect sizes. Statistical tests were based on 95% CIs. When the 95% CI contained 1 for RR, or the 95% CI included 0 for WMD, it indicated that there was no significant difference between the two rabies vaccines. Considering the universal heterogeneity of clinical and statistical methods between studies, we used random-effects models in both single-rate meta-analysis and NMA to ensure the rationality and universality of the pooled results. Begg's test was used to determine whether there was publication bias. When the p-value was < 0.05, publication bias existed.

Results

Literature search

A total of 1,591 articles, including 19 manually retrieved reports, were retrieved from the electronic databases. After removing duplicate entries, 1,105 articles were screened based on the title and abstract. Furthermore, 125 articles that met the screening criteria had entered the stage of "Full-text articles

assessed for eligibility." Finally, 27 qualified articles were included in the systematic review and meta-analysis, including which 17 RCTs, nine prospective observational studies and one retrospective study. The literature screening process is illustrated in Figure 1.

Research characteristics

Most of the studies included in the systematic review and meta-analysis were published over the past 20 years and were mainly distributed in Asia (China, India, Thailand, Iran, Pakistan, and the Philippines) and North America (the United States). A total of 18,630 subjects reported in the 27 documents[14–40] were included in the meta-analysis, most of whom were between 10 and 60 years old, and all had different categories of rabies exposure. Rabies exposure was mostly categorized as category II or above. The characteristics of individual studies are presented in Table 1. Details of exposure categories and use of RIG are displayed in **Stable 1**, but most were not reported.

In the included studies, selection bias, performance bias, detection bias, and attrition bias were considered to be low risk for those studies that clearly introduced the use of randomized, controlled, and blinded methods without loss of follow-up. Otherwise, they were considered to be at high risk or unclear. The risk of other biases is unclear in studies that were not designed and conducted following the principles of randomized, controlled, and blinded methods. There was no reporting bias in any of the included studies. The bias assessment results are summarized in Figure 2.

Safety

To describe the incidence of total ARs of the HDCV, PVRV, and PCECV in general, we first conducted a single-rate meta-analysis. The results are shown in Figure 3. Meta-analysis of single-rate data requires that the rate distribution follow a normal distribution as much as possible; hence, we performed an arcsine transformation of the original data that did not meet the normality. Data regarding the incidence of total ARs for HDCV, PVRV, and PCECV were obtained from seven,[15,27,30,36–39] three,[17,32,35] and seven[15,17,24,25,27,28,30] articles, respectively. The results showed that the pooled incidence of total AR of HDCV was 3.2% (95% CI: 0.9%–10.9%), that of PVRV was 11.7% (95% CI: 5.2%–24.1%), and that of PCECV was 26.0% (95% CI: 16.4%–38.7%). The pooled incidence of total ARs was 8.4% (95%CI: 4.1%–16.3%) for the combination of the three rabies vaccines.

Subsequently, we compared the incidence of solicited symptoms in local and systemic ARs. The results are shown in Table 2. The data used for conducting NMA were obtained from the studies by Bose,[18] Benjavongkulchai,[33] Fang,[20] Ashwathnarayana,[23] Ramezankhani,[19] Li,[14] Chen,[16] Lu,[29] and

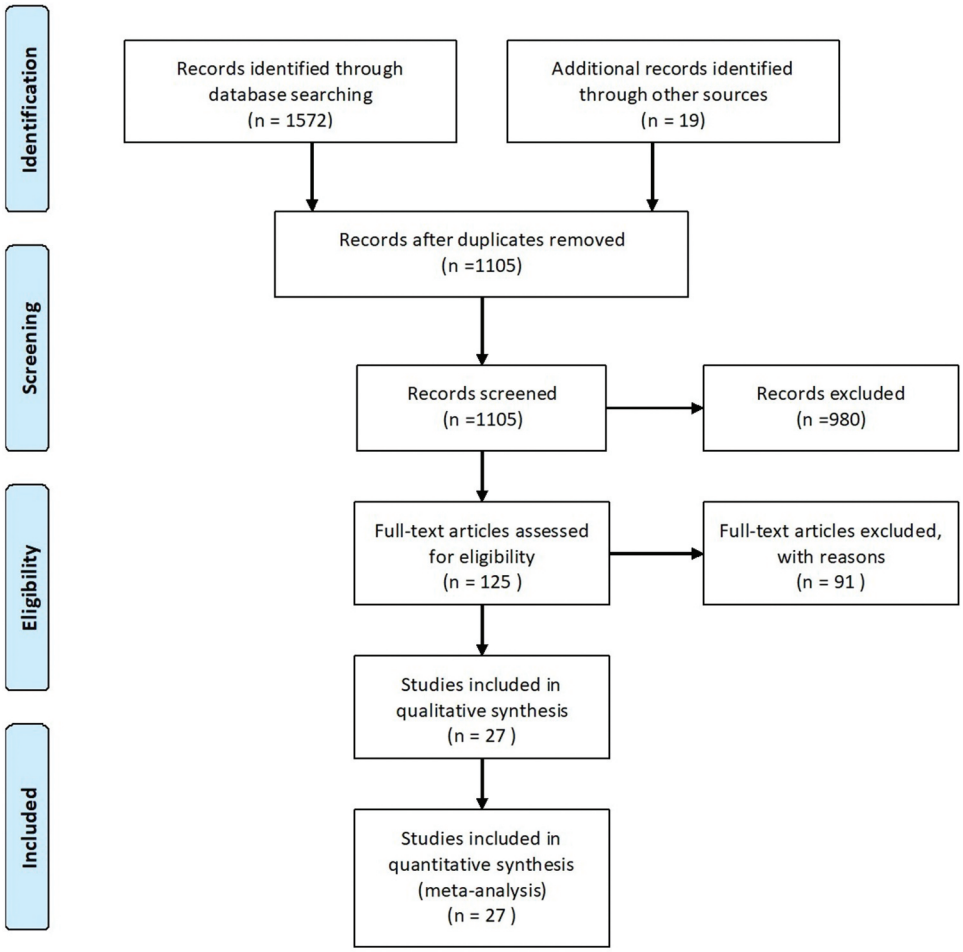

Figure 1. Flowchart of literature selection.

Table 1. Study characteristics.

Study	Year	Country	Study design[a]	Number	Sex ratio (Male/ Female)	Age	Categories of exposure	Vaccine name/ manufacturer	RIG[b]	Immunogenicity[c]	Safety[c]
PVRV[e]											
Li[14]	2020	China	RCT	150	0.92	10–60	NR[d]	NR	-	√	√
Fan[15]	2019	China	RCT	200	0.92	40 ± 26.7	NR	Guangzhou NuoCheng	NR	×	√
Chen[16]	2018	China	RCT	200	1.17	2–68	I & II	Guangzhou NuoCheng	-	×	√
Peng[17]	2016	China	RCT	869	NR	>2	II	NR	NR	×	√
Peng[17]	2016	China	RCT	941	NR	>2	II	NR	NR	×	√
Peng[17]	2016	China	RCT	881	NR	>2	II	NR	NR	×	√
Bose[18]	2016	India	RCT	60	3	5–77	II & III	Rabivax-S	±	√	√
Ramezankhani[19]	2016	Iran	RCT	702	3.74	26.8 ± 13.1	II & III	Verorab	NR	×	√
Fang[20]	2014	China	RCT	28	NR	19–60	II	Liaoning ChengDa	NR	√	√
Wang[21]	2011	China	RCT	200	0.63	6–67	NR	Speeda	NR	√	×
Wang[21]	2011	China	RCT	50	1.27	16–78	NR	Verorab	NR	√	×
Liu[22]	2011	China	RCT	30	0.88	22–57	NR	SPEEDA	NR	√	√
Ashwathnarayana[23]	2009	India	RCT	50	5.25	8–55	II & III	Verorab	±	√	√
Shu[24]	2007	China	RCT	300	NR	>2	II & III	Liaoning ShengWu	-	×	√
Shu[24]	2007	China	RCT	300	NR	>2	II & III	Changchun ChangSheng	-	×	√
Cao[25]	2007	China	RCT	1250	0.69	2–80	I & II	Liaoning ChengDa	-	×	√
Cao[25]	2007	China	RCT	1180	0.97	2–80	I & II	Verorab	-	×	√
Sampath[26]	2005	Pakistan	RCT	75	NR	NR	II	Abhayrab	-	√	×
Sampath[26]	2005	Pakistan	RCT	67	NR	NR	III	Abhayrab	-	√	×
Sampath[26]	2005	Pakistan	RCT	88	NR	NR	III	Abhayrab	+	√	×
Huang[27]	2018	China	P. O.	58	2.22	NR	NR	NR	NR	×	√
Liu[28]	2012	China	P. O.	398	1.17	2–67	NR	Verorab	-	√	√
Lu[29]	2010	China	P. O.	300	0.99	3–65	II	Verorab	-	×	√
Niu[30]	2019	China	R. O.	5347	NR	NR	NR	Changchun ChangSheng	NR	×	√
PCECV[f]											
Peng[17]	2016	China	RCT	813	NR	>2	II	NR	NR	×	√
Bose[18]	2016	India	RCT	60	2.75	5–77	II & III	Rabipur	±	√	√
Ramezankhani[19]	2016	Iran	RCT	747	4.7	27.4 ± 13.9	II & III	Rabipur	NR	×	√
Fang[20]	2014	China	RCT	28	NR	19–60	II	Rabipur	NR	√	√
Shao[31]	2013	China	RCT	400	NR	18–59	II & III	Rabipur	NR	√	√
Ashwathnarayana[23]	2009	India	RCT	50	4	7–48	II & III	Rabipur	±	√	√
D.J. Briggs[32]	2000	Thailand	RCT	57	0.97	5–66	II & III	NR	±	√	√
Benjavongkulchai[33]	1997	Thailand	RCT	17	NR	NR	I & II	Kaketsuken	-	√	√
Benjavongkulchai[33]	1997	Thailand	RCT	21	NR	NR	III	Kaketsuken	+	√	√
Benjavongkulchai[33]	1997	Thailand	RCT	21	NR	NR	III	Kaketsuken	+	√	√
Sirikun[34]	2018	Thailand	P. O.	29	0.45	19–73	III	Rabipur	+	√	√
Narayana[35]	2014	India	P. O.	129	3.61	18–55	II & III	Vaxirab-N	±	√	√
Lu[29]	2010	China	P. O.	300	0.95	3–65	II	NuoHua	-	×	√
HDCV[g]											
Li[14]	2020	China	RCT	150	0.86	12–60	NR	NR	-	√	√
Fan[15]	2019	China	RCT	200	0.56	43 ± 28.9	NR	Chendu KangHua	-	×	√
Chen[16]	2018	China	RCT	200	1.3	2–68	I & II	Kanghua	-	×	√
Sudarshan[36]	2008	India	RCT	29	4	15–55	II & III	Rabivax	±	√	√
Sudarshan[36]	2008	India	RCT	16	4	15–55	II & III	MIRV	±	√	√
Sudarshan[36]	2008	India	RCT	148	3.11	5–55	II & III	Rabivax	±	√	√
Benjavongkulchai[33]	1997	Thailand	RCT	39	NR	NR	III	NR	+	√	√
Yan[37]	2018	China	P. O.	700	NR	7–60	NR	Kanghua	±	×	√
Huang[27]	2018	China	P. O.	53	1.79	NR	NR	NR	NR	×	√
Wilde[38]	1995	Thailand	P. O.	100	2.13	2–60	III	NR	±	√	√
Anderson[39]	1980	America	P. O.	90	1.5	1–83	NR	Wyeth Laboratories	+	√	√
Bahmanyar[40]	1976	Iran	P. O.	45	3.1	3–90	NR	Institute Merieux	±	√	×
Niu[30]	2019	China	R. O.	464	NR	NR	NR	Kanghua	NR	×	√

a: RCT represents randomized controlled trial; P. O. represents reprospective observational; R. O. represents retrospective observational. b: RIG represents rabies immunoglobulin; "-" represents no injection of RIG; "+" represents injection of RIG; "±" represents injection of RIG for part of the subjects. c: "√" represents the study provide corresponding data; "×" represents not. d: NR represent not reported. e: PVRV represents purified Vero cell vaccine. f: PCECV represents purified chick embryo cell vaccine. g: HDCV represents human diploid cell vaccine.

Huang.[27] Comparing the HDCV and PVRV vaccines, we found that there was a statistically significant difference in the incidence of one local symptom and two systemic symptoms: local pain (RR = 0.51, 95% CI: 0.21–0.98), fever (RR = 0.20, 95% CI: 0.03–0.64), and weakness (RR = 0.25, 95% CI: 0.06–0.73). Thus, the incidence of local pain, fever, and weakness for HDCV were about one-half, one-fifth, and one-quarter of that for PVRV, respectively. Comparing HDCV and PCECV vaccines, we found statistically significant differences in the incidence of one local symptom and one systemic symptom: local pain (RR = 0.49, 95% CI: 0.20–0.95) and fever (RR = 0.27, 95% CI: 0.03–0.92). The incidence of local pain and fever for HDCV was approximately one-half and one-quarter that of PCECV, respectively. Comparing PVRV and PCECV, there was no

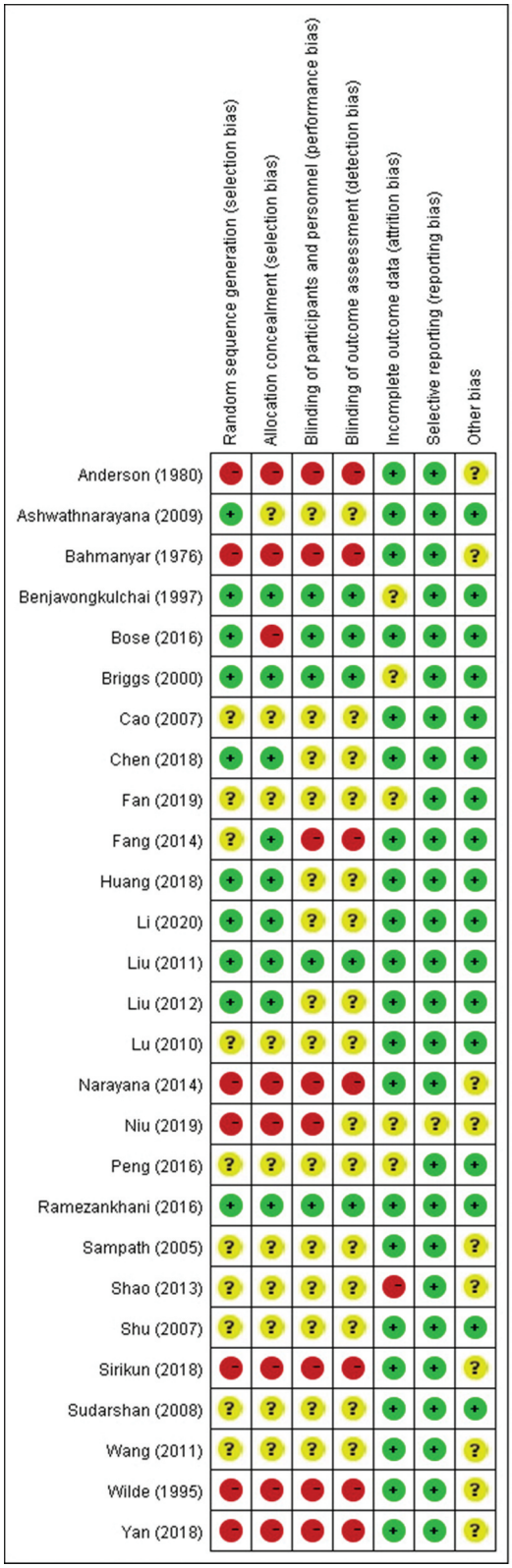

Figure 2. Quality assessment of included studies. "+" represents low risk of bias; "?" represents unclear risk of bias; "-" represents high risk of bias.

significant difference in the incidence of any local and systemic symptoms, which indicated that the safety of the two was equivalent.

Immunogenicity

This study mainly focused on the seroconversion rate on day 7 and the RVNA titer or concentration on day 14. The data of seroconversion on day 7 of HDCV, PVRV, and PCECV were obtained from five,[14,33,38–40] six,[14,18,20–22,26] and five[18,20,31,33,34] articles, respectively. Single-rate meta-analysis results (Figure 4) showed that the pooled seroconversion rate of HDCV was 35.7% (95% CI: 8.6%–69.3%), that of PVRV was 55.6% (95% CI: 22.6%–86.2%), and that of PCECV was 58.3% (95% CI: 15.0%–94.7%). The pooled seroconversion rate for the combination of the three rabies vaccines was 50.4% (95% CI: 29.6%–71.1%) for the combination of the three rabies vaccines. A total of three studies provided comparative results for RVNA titer or concentration for two rabies vaccines, among which Bose[18] and Ashwathnarayana[23] compared PVRV and PCECV, while Li[14] compared HDCV and PVRV. The results of the adjusted indirect comparisons showed that there were no significant differences between HDCV and PVRV (WMD = 0.03, 95% CI = −0.26–0.32), HDCV and PCECV (WMD = 0.16, 95% CI = −0.17–0.49), and PVRV and PCECV (WMD = 0.13, 95% CI = −0.03–0.28).

Assessment of publication bias

Begg's test was performed to identify whether there was publication bias or not in the studies used for conducting single-rate meta-analysis and NMA. All the p values were > 0.05, which indicating that the null hypothesis of funnel plot symmetry was not rejected. In other words, there was no publication bias.

Discussion

In this study, we performed a meta-analysis of immunogenicity and safety of three rabies vaccines widely administered to humans for immunization against rabies. The purpose and time of rabies vaccination can be divided into PrEP and PEP. PrEP is often applied to occupational populations or travelers with a high risk of rabies infection, or in epidemic areas of a rabies outbreaks.[41] However, PEP is more common in daily life. Unlike for that in PrEP, vaccination is possibly the only life-saving option for post-exposure rabies populations. Therefore, although vaccination is only required for rabies exposures of category II and above according to WHO recommendations,[4] it is not uncommon for people to receive rabies vaccination unnecessarily. In addition, both PrEP and PEP use rabies vaccine to induce fundamental immunity, whereas the vaccination regimens are entirely different. Based on the above considerations, we paid more attention to the post-exposure populations and excluded the studies based on healthy populations. Moreover, studies[42,43] have shown that if individuals with a history of rabies vaccination are vaccinated again, the induced immune response levels are different from that of the initial vaccination. Therefore, individuals with a history of rabies vaccination were excluded from this study to minimize clinical heterogeneity between studies.

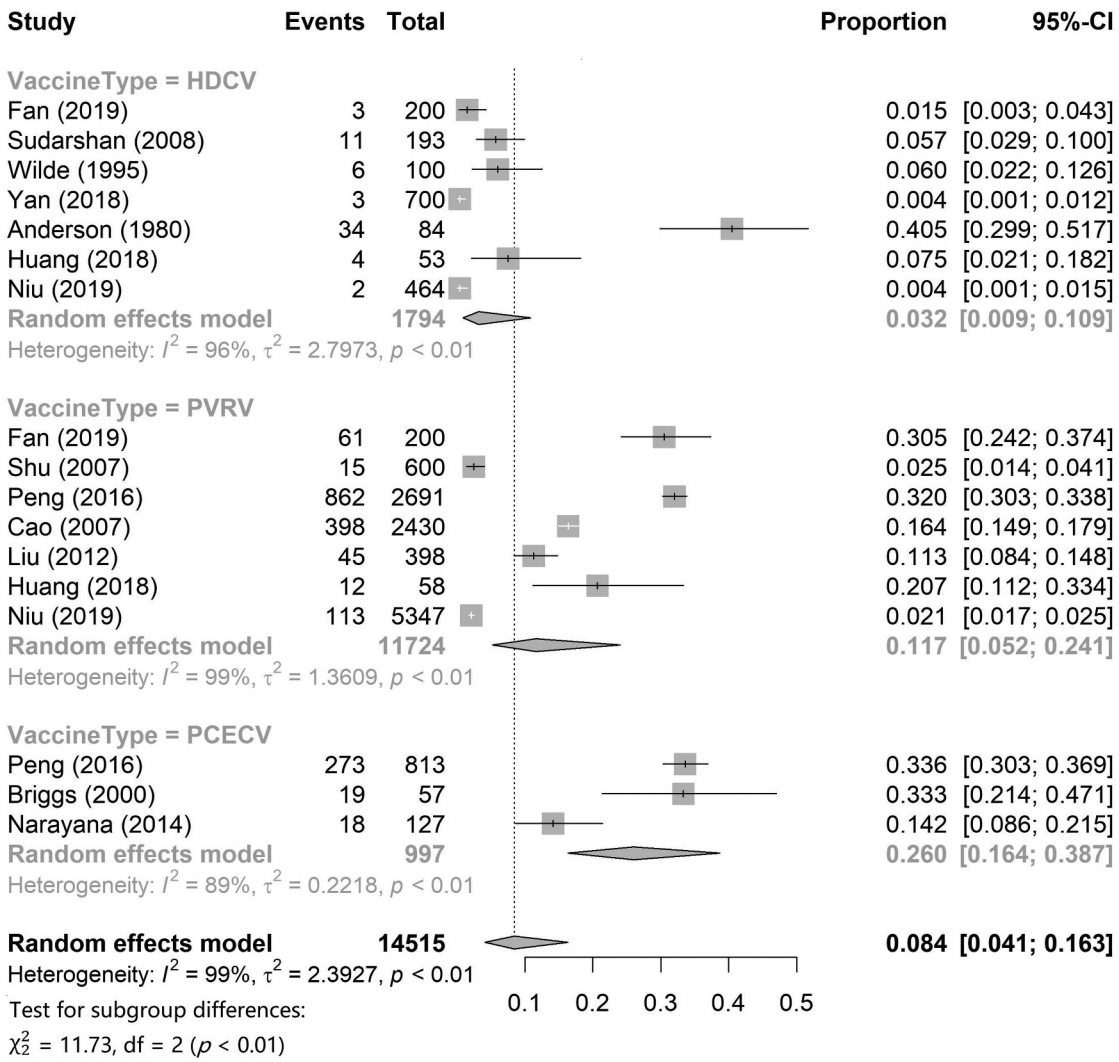

Figure 3. The pooled incidence of total ARs of HDCV, PVRV and PCECV.

Immunogenicity and safety are two essential aspects for evaluating the merits and demerits of rabies vaccines. Factors affecting the immunogenicity and safety of rabies vaccines mainly include the nature of the vaccine itself, the characteristics of the individual vaccinated, and the vaccination regimen. A meta-analysis study previously compared differences in immunogenicity and safety between different vaccination regimens.[5] However, no systemic review or meta-analysis compares the differences in immunogenicity and safety between different cell-culture rabies vaccines. The first rabies vaccine was developed more than a 100 years ago and since then different kinds of rabies vaccines have been released. The earliest neural tissue-derived vaccines (NTV) represented by the Pasteur vaccine have been eliminated because of their high incidence of neurological complications, long immune cycle, frequent injections, slow immune responses, and poor protective efficacy.[44] Subsequently, most embryo-culture vaccines were also eliminated because of high AR rates and poor protective effects; only some of them are still produced because of their more straightforward manufacturing processes and lower costs, such as PCECV.[45] Currently, most countries and regions have adopted cell-culture rabies vaccines represented by PVRV and HDCV. Theoretically, the advantage of cell-culture vaccines is that rabies viruses from cell culture are easy to purify because the culture system has a single cell type and fewer impurities.[46] Therefore, the cell-culture vaccines have the advantages of high potency, good immune effects, and low price. However, although these three rabies vaccines have been applied clinically for decades, to date, no research has summarized and compared their safety and immunogenicity. Hence, we have evaluated the safety and immunogenicity of three currently marketed rabies vaccines used in PEP, with the aim of providing a scientific basis for policy formulation and clinical practice. In addition, studies[47–49] have shown that RIG does not affect the safety and immunogenicity of rabies vaccines; thus, we did not conduct a subgroup analysis according to RIG.

Single-rate meta-analysis is a simple combination of the incidence of outcomes of interest, which has the advantage of being more flexible in terms of study types. Although it is not possible to directly provide an estimate of RR, we can make full use of existing data to initially compare the safety and immunogenicity of the three rabies vaccines with the help of the single-rate meta-analysis method.[50] Furthermore, direct and

Table 2. Multiple comparisons of 3 rabies vaccines about safety and immunogenicity (Case/Total).

		Safety									Immunogenicity (D14)[a]	
		Local AR					Systemic AR					
Study	Vaccine type	Local pain	Erythema	Pruritus	Edema	Induration	Headache	Fever	Myalgia	Weakness	Sero conversion	RVNA titer [GMT(95%CI) /Subjects, IU/ml]
Benjavongkulchai (1997)	PCECV	13/72	1/72	0/72	0/72	0/72	1/72	16/72	15/72	0/72	55/55	1.86(NR)/22
Benjavongkulchai (1997)	HDCV	3/40	1/40	0/40	0/40	0/40	1/40	0/40	0/40	0/40	38/39	3.10(NR)/39
Fang (2014)	PVRV	0/28	0/28	0/28	1/28	0/28	0/28	1/28	0/28	0/28	NR[b]	NR
Fang (2014)	PCECV	2/33	0/33	0/33	1/33	0/33	0/33	1/33	0/33	0/33	NR	NR
Bose (2016), 1	PVRV	20/30	3/30	2/30	2/30	5/30	7/30	4/30	3/30	11/30	27/27	20.57(17.03 ~ 24.84)/27
Bose (2016), 1	PCECV	21/31	0/31	3/31	3/31	4/31	5/31	2/31	5/31	9/31	29/29	16.01(12.46 ~ 20.57)/29
Bose (2016), 2	PVRV	13/30	0/30	1/30	1/30	1/30	5/30	1/30	2/30	7/30	27/27	16.47(13.39 ~ 20.26)/27
Bose (2016), 2	PCECV	9/31	0/31	0/31	1/31	1/31	2/31	0/31	2/31	4/31	29/29	14.13(11.42 ~ 17.47)/29
Ashwathnarayana (2009)	PCECV	1/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	50/50	6.88(6.11 ~ 7.75)/50
Ashwathnarayana (2009)	PVRV	1/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	48/48	6.65(5.91 ~ 7.49)/48
Ramezankhani (2016)	PVRV	27/702	9/702	7/702	4/702	0/702	8/702	11/702	6/702	5/702	NR	NR
Ramezankhani (2016)	PCECV	28/747	8/747	1/747	2/747	0/747	16/747	10/747	5/747	11/747	NR	NR
Li (2020)	HDCV	6/150	0/150	2/150	3/150	2/150	4/150	3/150	1/150	0/150	149/150	21.47(18.91 ~ 24.36)/150
Li (2020)	PVRV	7/150	0/150	1/150	3/150	1/150	4/150	3/150	0/150	1/150	148/150	20.78(18.21 ~ 23.71)/150
Chen (2018)	HDCV	7/200	2/200	2/200	2/200	5/200	1/200	3/200	0/200	5/200	NR	NR
Chen (2018)	PVRV	11/200	5/200	6/200	5/200	4/200	6/200	25/200	1/200	26/200	NR	NR
Lu (2010)	PCECV	19/300	1/300	11/300	1/300	4/300	4/300	3/300	0/300	8/300	NR	NR
Lu (2010)	PVRV	15/300	1/300	13/300	1/300	4/300	5/300	4/300	0/300	9/300	NR	NR
Huang (2018)	HDCV	1/53	0/53	0/53	0/53	0/53	1/53	1/53	0/53	1/53	NR	NR
Huang (2018)	PVRV	5/58	0/58	0/58	0/58	0/58	1/58	2/58	0/58	3/58	NR	NR
Pooled PVRV		99/1548	18/1548	31/1548	17/1548	15/1548	36/1548	51/1548	12/1548	62/1548	250/252	-
Pooled PCECV		93/1264	10/1264	16/1264	8/1264	9/1264	28/1264	32/1264	27/1264	32/1264	163/168	-
Pooled HDCV		17/443	3/443	4/443	5/443	7/443	7/443	7/443	1/443	6/443	263/267	-
RR, 95%CI (HDCV vs. PVRV)		0.51 (0.20 ~ 0.98)*	0.79 (0.12 ~ 2.63)	1.15 (0.17 ~ 3.72)	1.04 (0.26 ~ 2.83)	1.82 (0.41 ~ 5.19)	0.74 (0.15 ~ 2.36)	0.20 (0.03 ~ 0.64)*	0.46 (0.02 ~ 2.10)	0.25 (0.06 ~ 0.73)*	1.00 (0.75 ~ 1.34)	0.03 (−0.26 ~ 0.32)
RR, 95%CI (HDCV vs. PCECV)		0.49 (0.20 ~ 0.95)*	1.58 (0.19 ~ 5.79)	2.35 (0.24 ~ 9.99)	1.33 (0.20 ~ 4.73)	2.24 (0.38 ~ 6.86)	1.60 (0.24 ~ 5.73)	0.27 (0.03 ~ 0.92)*	0.32 (0.01 ~ 1.36)	0.48 (0.08 ~ 1.65)	1.00 (0.68 ~ 1.46)	0.16 (−0.17 ~ 0.49)
RR, 95%CI (PVRV vs. PCECV)		1.08 (0.65 ~ 1.87)	0.71 (0.19 ~ 1.67)	0.67 (0.18 ~ 1.66)	1.07 (0.29 ~ 2.62)	0.98 (0.34 ~ 2.25)	0.57 (0.17 ~ 1.35)	1.07 (0.27 ~ 2.91)	1.82 (0.41 ~ 5.85)	0.61 (0.24 ~ 1.21)	1.00 (0.71 ~ 1.39)	0.13 (−0.03 ~ 0.28)

a: Immunogenicity data were obtained 14 days after the first vaccination dose. b: NR represents not reported. *: Difference was statistically significant.

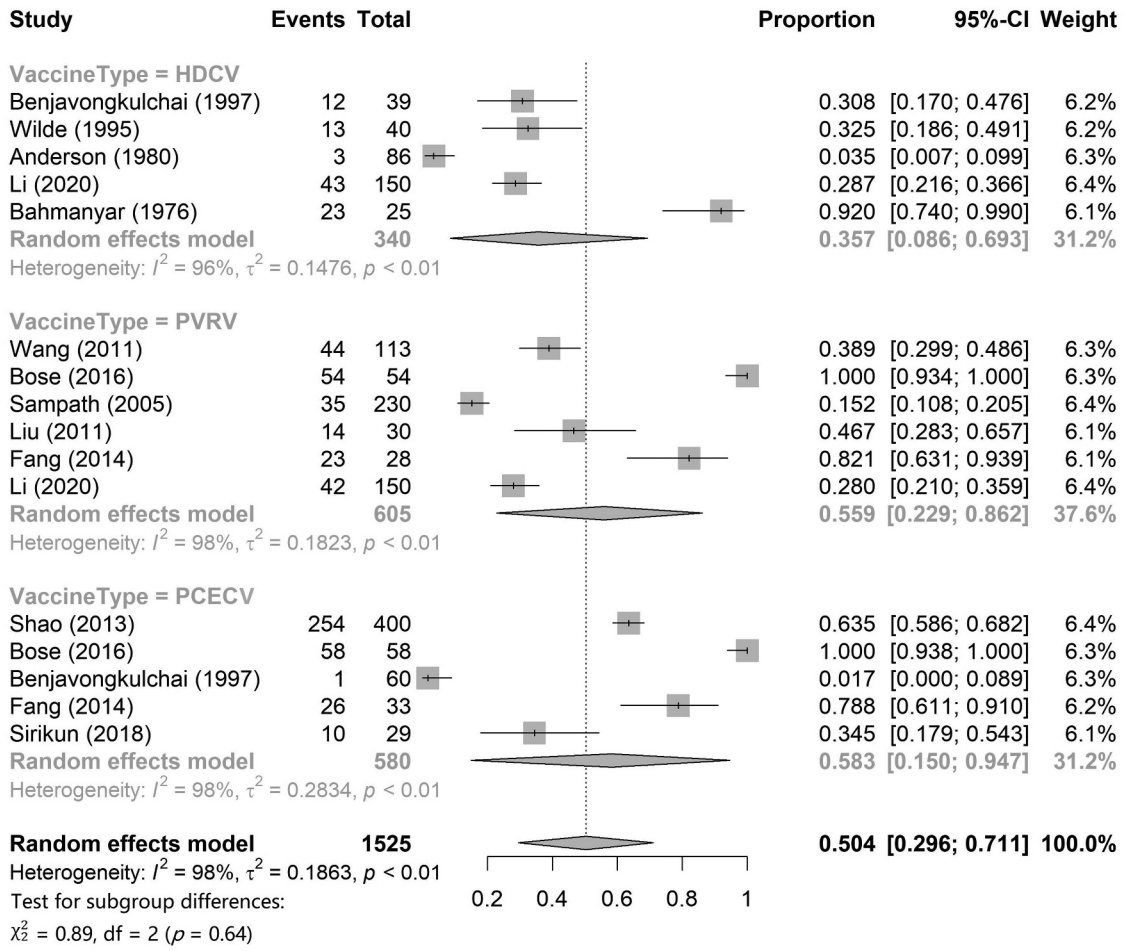

Figure 4. Pooled seroconversion rates on day 7 of HDCV, PVRV and PCECV.

indirect evidence were combined by NMA in the research network to compare the safety and immunogenicity of the three rabies vaccines in a single analysis. The advantage of NMA is that it can estimate the relative effect of any two interventions in the network, which is usually more accurate than a single direct or indirect estimate. It also allows for an estimate of the level and level of intervention.[51]

In terms of safety, the results of a single-rate meta-analysis showed that the pooled incidence of total ARs to HDCV was 5.8% (95% CI: 1.3%–12.5%), which was significantly lower than that of PCECV, but not significantly different from PVRV. HDCV is cultured from human diploid cells, while both PVRV and PCECV are cultured from animal cells. From the perspective of the principles of vaccine manufacture and immunological theories, HDCV contains fewer allogeneic substances and does not contain allogeneic acids, resulting in fewer ARs after vaccination.[52] Compared with PCECV, although PVRV was lower than PCECV in the point estimates, the results of the two interval estimates were overlapped, and there was no factor which indicated that the pooled incidence of total ARs to PVRV was significantly lower than that of PCECV. A sample size of 11,724 was used to calculate the pooled incidence of total ARs to PVRV, while HDCV and PCECV comprised only 1,794 and 997, respectively. Therefore, it will be necessary to increase the HDCV and PCECV participant sample size to obtain more stable results. To further explore which specific AR symptoms were different, we compared the differences in five local symptoms and four systemic ones among the three vaccines by NMA. The results showed no significant differences in AR symptoms between the three vaccines, except for local pain, fever, and weakness. The incidence of local pain and fever were significantly lower in HDCV than in PVRV and PCECV. As for the incidence of weakness, HDCV was significantly lower than PVRV, but the difference between PCECV and HDCV was not statistically significant. Therefore, in terms of AR symptoms, HDCV was safer than the other two rabies vaccines, which was primarily reflected in the lower incidence of local pain, fever, and weakness after vaccination.

It is notable that no deaths from rabies were reported in the studies included in this review. With RVNA ≥ 0.5 IU/mL representing the standard for seropositivity, the seroconversion rates were very close to 100% after day 7 in almost every study (**S**Table 2), indicating that the protective rate of the three types of rabies vaccines can reach nearly 100% below the premise of scientifically and effectively delivering rabies vaccines. The seroconversion rate on day 7 and RVNA titer or concentration on day 14 were used as measurable variables to compare the immunogenicity of the three rabies vaccines. For this reason, complete data concerning immunogenicity after a full five-dose vaccination series were not often easy to obtain because of poor

compliance; thus, most vaccine studies selected day 14 (i.e. after the third dose and before the fourth dose) as a crucial timepoint for immunogenicity assessment, for both PEP and PrEP.[18,36,53] In addition, short-term immunogenicity of rabies vaccine is more important for PEP compared with PrEP, because exposed people must reach a sufficiently high RVNA level in a short time to neutralize the rabies virus. Hence, we thought that discussing the immune effect of a full five-dose vaccine was not significant for the three rabies vaccines; instead, it was much more noteworthy to discuss the short-term immunogenicity of the three rabies vaccines on days 7 and 14. The results showed that the 95% CIs for pooled seroconversion rates on day 7 for the three rabies vaccines overlapped with each other, and a significant differences were not observed. The same results were obtained when performing NMA for RVNA titer or concentration on day 14 as the measurement variable. Therefore, HDCV, PVRV, and PCECV effectively prevented rabies, and their immunogenicity levels were similar. However, the broad range of 95% CIs of pairwise comparisons suggested that an insufficient sample size might lead to false-negative results in such comparisons. Hence, further studies are required that can address this limitation.

In conclusion, HDCV, which exhibited good safety and immunogenicity is worthy of being recommended first for PEP. Although the immunogenicity of PVRV and PCECV is not significantly different from that of HDCV, there are elevated risks of local pain and fever after vaccination, and greater caution should be exercised in actual applications. For a prolonged time, HDCV has had limited use in developing countries owing to technical difficulties and high prices.[54] In recent years, the perfusion bioreactor based on microcarrier technology created by Chengda Biotechnology Co. has greatly reduced the cultivation period of HDC and increased the production capacity of HDCVs. It is believed that with the launch and large-scale production of domestic HDCV in China, the cost of HDCV applications on a global scale will be significantly reduced, enabling further promotion and application of this safe and effective vaccine.

However, the current study had certain limitations. First, immunogenicity data were only collected and analyzed for days 7 and 14 after the first dose. More immunogenicity data at other time points are needed, especially for RVNA titer, based on more PEP research for the three vaccines in the future. Notwithstanding the insufficient long-term immunogenicity data in studies meeting our inclusion and exclusion criteria, substantial clinical practices have demonstrated the satisfying long-term effectiveness of all the three vaccines. Second, the variety of measurable variables and the lack of documentation have in a shortage of subjects included in the NMA. Furthermore, due to the small number of studies used for multiple comparisons, the assessment results of publication bias may be unreliable. Third, rapid fluorescence focus inhibition tests (RFFITs) were used in most studies, while other methods were used in a small number of studies, such as the mouse neutralization tests (MNTs) and enzyme-linked immunosorbent assays (ELASAs), which might lead to heterogeneity.

Disclosure statement

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