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Global perspectives on smallpox vaccine against monkeypox: a comprehensive meta-analysis and systematic review of effectiveness, protection, safety and cross-immunogenicity

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ABSTRACT

A large outbreak of monkeypox occurred in 2022, and most people lack immunity to orthopoxvirus. Smallpox vaccination is essential for preventing further smallpox outbreaks. This study evaluated the effectiveness, protection, safety, and cross-immunogenicity of smallpox vaccine in preventing monkeypox infection. PubMed, Embase, Scopus, and Web of Science were searched from database inception to 10 March 2024. We included studies involving "monkeypox virus" and "vaccinations", and excluded reviews, animal studies, and articles with missing or duplicate data. A total of 37 studies with 57,693 participants were included in the final analysis. The effectiveness data showed that monkeypox infection rates were lower in the smallpox-vaccinated group than in the unvaccinated group (risk ratio [RR]: 0.46; 95% confidence interval [CI]: 0.31–0.68). The protection data showed that smallpox vaccination effectively reduced the risk of severe monkeypox infection (RR: 0.61; 95% CI: 0.42–0.87). Third-generation vaccines showed greater efficacy (RR: 0.36, 95% CI: 0.22–0.56) than first-generation vaccines. The number of doses of smallpox vaccine has no significant effect on monkeypox. Safety data showed that adverse reactions after smallpox vaccination were mainly mild and included local erythema, swelling, induration, itching, and pain. Meanwhile, we found that smallpox vaccination could induce the production of neutralizing antibodies against monkeypox. Our findings offer compelling evidence supporting the clinical application of the smallpox vaccine for preventing monkeypox and advocate that high-risk groups should be prioritized for receiving one dose of the smallpox vaccine if the vaccine stockpile is low.

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KEYWORDS Monkeypox; smallpox; vaccine; effectiveness; safety; immunogenicity

Introduction

The monkeypox (mpox) virus (MPXV) is a DNA virus belonging to the *Orthopoxvirus* (OPXV) genus [1,2]. The genus encompasses many other poxviruses, including smallpox, vaccinia, cowpox, and camelpox viruses, as well as more recently isolated poxviruses [3]. Previously, mpox was endemic to Central and West Africa [4,5]; but had recently become a global epidemic. Between 2017 and 2018, a large outbreak of mpox was reported in Nigeria [6], and five cases were reported in the United Kingdom, Israel, and Singapore during the same period [7]. From January 2022 to April 2024, a total of 95,226 mpox cases were reported by the World Health Organization (WHO) from 117 countries [8]. Owing to the significant rise in global mpox cases in recent years, WHO has declared the mpox outbreak a global health emergency [9].

The incubation period of MPXV infection ranges from 5 to 21 days, and the common symptoms include fever and skin lesions, which are relatively similar to those of smallpox; however, one feature that distinguishes mpox from smallpox is lymphadenopathy [10]. Mpox is often a self-limiting disease, with symptoms lasting 2–4 weeks; nonetheless, severe cases and death can occur. The severity of disease caused by different strains varies, with mortality rates ranging from 1% to 10%, as reported in multiple studies [11–13]. Individuals infected with human immunodeficiency virus (HIV) and those not vaccinated against smallpox are at a higher risk of death [14]. Moreover, men who have sex

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with men (MSM) or are identified as bisexuals, as well as those with sexually transmitted diseases, are reported to be at a high risk of MPXV infection [15]. Of the cases reported from 2022 to 2024 with available data, 85.5% of mpox cases occurred in MSM, and 51.9% of patients with mpox were co-infected with HIV [8]. The high prevalence of HIV co-infection means that approximately half of monkeypox patients are at risk of developing severe illnesses [16]. Owing to the global outbreak of mpox and the occurrence of severe and fatal cases, the idea of control of the epidemic should be clarified.

Owing to the lack of specific drugs, no effective clinical treatments are available for mpox. Preventive strategies based on the development of the mpox vaccines have become a crucial public health management strategy for coping with emerging infectious diseases. MPXV has antigenic similarity to vaccinia virus (VACV) [17]; thus, the smallpox vaccine may provide cross-protection against mpox. Several decades ago, the smallpox vaccine was shown to have an effect on mpox, and one study reported no deaths among those vaccinated with the smallpox vaccine, whereas the fatality rate among unvaccinated patients was 11% [10]. Earlier epidemiological research in the Democratic Republic of the Congo found that people who had been vaccinated against smallpox had a 5.2-fold lower risk of mpox than unvaccinated people [18]. However, the above studies had geographical limitations, and the mode of transmission and high-risk groups of infection were different from today's outbreaks. More importantly, smallpox was declared eradicated in 1980. Consequently, an increasing number of people lack cross-protection from orthopoxvirus, making the population generally susceptible to MPXV. In the current outbreak, men aged 18–44 years were the most severely affected by the outbreak, accounting for 79.4% of the reported cases [8]. Therefore, to prevent the further spread of mpox, more evidence on the cross-protection of vaccines and urgent smallpox vaccination for high-risk groups are needed.

Currently, studies have reported a 35%–85% effectiveness of the smallpox vaccine in preventing mpox, with a low incidence of adverse events [19,20]. Some countries have approved smallpox vaccination as an emergency measure to prevent mpox based on data from existing studies [21,22]. Although several studies have evaluated the effectiveness and safety of the smallpox vaccines against mpox, a summary of these studies is necessary to reach a more comprehensive and credible conclusion. Therefore, this systematic review and meta-analysis aimed to summarize the current studies on smallpox vaccines against MPXV infection; assess the effectiveness, protection, safety, and cross-immunogenicity of smallpox vaccines against MPXV infection in the real world; and provide evidence for the widespread use of smallpox vaccines against MPXV infection and guidance for the vaccination protocols.

Methods

Protocol and registration

This research protocol follows the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Multimedia Appendix 1) and has been recorded in the Prospective International Registry of Systematic Reviews (PROSPERO) database (CRD42024536542).

Search strategy

A comprehensive search strategy comprising phrases related to "monkeypox virus" and "vaccinations" was used to search PubMed, Embase, Scopus, and Web of Science for all articles from the inception of each database through 10 March 2024. This analysis considered only papers published in English. Additional information regarding the search approach can be found in Multimedia Appendix 2. Following the removal of duplicates, two authors conducted separate screenings of the titles, abstracts, and full-text studies. Disagreements were handled by engaging in discourse and ultimately reaching a consensus.

Eligibility criteria

The inclusion criteria were as follows: (1) study design, randomized clinical trials (RCTs), cross-sectional studies, cohort studies, case–control studies, and serological studies; (2) study population, all age groups; (3) intervention, get vaccinated against smallpox; and (4) endpoints, infection status, safety data, and antibody responses against MPXV. Pregnant and lactating women were excluded from the study. We excluded reviews, conference abstracts, case reports, letters, animal studies, irretrievable full-text research, and other articles that did not address the research issue. Only the latest or most comprehensive data were included when duplicates were detected. According to the WHO interim guidance, a positive polymerase chain reaction (PCR) test for OPXV, and confirmation of MPXV infection is established using PCR and/or sequencing, or by obtaining a positive MPXV PCR test in a suspected case [23]. Mild cases of mpox were defined as cases with 1–2 systemic symptoms and/or skin lesions on only one body location and/or $\leq$ 25 systemic skin lesions. Severe mpox cases were defined as those with $\geq$ 3 systemic symptoms and/or skin lesions on > 2 body locations and/or >

25 systemic skin lesions and/or hospitalization due to MPXV infection. The safety outcome was any adverse events occurring within 28 days of vaccination.

Data extraction and risk of bias assessment

Data were extracted from each study using Microsoft Excel. We obtained the following pertinent information: (1) general information, including author's name, year of publication, study area, study duration, and the number of participants; (2) study parameters, including study design and intervention programme; (3) participant characteristics; and (4) outcomes, including effectiveness data, protection data, and safety data.

The Cochrane risk of bias tool was used to evaluate the potential for bias in RCTs. Findings were categorized into three groups based on the level of bias: low, unclear, or high. The Newcastle-Ottawa Quality Assessment Scale was used to evaluate the potential for bias in the observational research, encompassing cross-sectional studies, cohort studies, and case–control studies. Findings were categorized as low, medium, or high bias. Two reviewers independently conducted the data extraction and evaluated the potential for bias. The risk-of-bias assessment details are presented in Multimedia Appendix 3.

Statistical analysis

Statistical analyses were conducted using the RevMan statistical software (version 5.4; The Cochrane Collaboration) and STATA MP statistical software (version 18.0). Graphical editing and presentation were performed using Adobe Illustrator (version 27.8.1). Dichotomous data was expressed using effect size (ES) and risk ratio (RR) values. A forest plot was used to calculate the cumulative impacts. The I^2 test was used to demonstrate significant heterogeneity. Four levels of heterogeneity were identified as 0%–40%, 30%–60%, 50%–90%, and 75%–100% and considered as insignificantly, moderately, significantly, and highly different, respectively. A subgroup analysis was employed to examine the potential variability within the data. If relevant, a leave-one-out sensitivity analysis was conducted to examine the consistency of the results. If an adequate number of articles were accessible, the presence of publication bias was examined using funnel plots and the Egger's test.

Results

Study selection and characteristics

A total of 7,024 studies were retrieved from the four different databases: 2,031 from Embase, 1,143 from PubMed, 1,862 from Scopus, and 1,988 from Web of Science. After removing duplicates, 2,799 studies remained. After evaluating the titles and abstracts, a total of 80 papers were selected for full-text review. In addition, 37 studies that met our specified criteria were ultimately selected for data analysis and systematic review: 11 studies on vaccine effectiveness, 7 studies on vaccine protection (one of which coincided with studies on vaccine effectiveness), 10 studies on vaccine safety, and 12 studies on vaccine cross-immunogenicity (two of which coincided with studies on safety). Figure 1 illustrates the literature search process.

We included studies from the United States, Italy, Germany, Canada, Spain, the Netherlands, Japan, South Korea, China, Belgium, Israel, and Central Africa. The study population comprised patients with mpox, high-risk populations, vaccine recipients, and healthy individuals. This study included 57,693 participants. The age of the participants ranged from 1 to 87 years. Further details on the study type, intervention protocol, vaccine type, dose, and study duration are provided in Table 1.

The included articles comprised 7 cross-sectional studies, 18 case–control or cohort studies, 2 RCTs, and 10 serological studies. The bias risk assessment showed that among the studies [19,20,24–48] included in the data analysis, 23 had a low risk of bias, whereas the other 4 [35,37,46,47] had a medium risk of bias (Figures S1–2, Table S1 in Multimedia Appendix 3).

Effectiveness

We pooled data from 11 studies on the effectiveness of the smallpox vaccine in preventing MPXV infection. In total, 13,505 vaccinated and 19,786 unvaccinated participants were included in the effectiveness analysis. The results showed that the risk of MPXV infection was reduced by 54% (RR: 0.46, 95% confidence interval [CI]: 0.31–0.68; Figure 2) with smallpox vaccination compared with that without smallpox vaccination [19,20,24–32].

Depending on the high heterogeneity, subgroup analyses were performed according to study region, vaccine dose, and sample size (Figure S3–5 in Multimedia Appendix 4). Analysis of data by region showed that, in North America, the risk of MPXV infection was 49% (RR: 0.51, 95% CI: 0.31–0.81) lower with vaccination than without vaccination [19,20,25–28,31]. In Europe, vaccination reduced the risk of infection by 60% (RR: 0.40, 95% CI: 0.17–0.91) [29,30,32]. In one study in Africa, smallpox vaccine reduced the infection risk by 69% (RR: 0.31, 95% CI: 0.11–0.83) [24]. Analysis of data by dose showed that completing only one dose of vaccination reduced the risk of MPXV infection by 39% (RR: 0.61, 95% CI: 0.33–1.12) [24,27–32], whereas full administration of two doses reduced the risk by 82% (RR: 0.18, 95% CI: 0.08–0.38) [19,20,25,26]. In addition, two studies

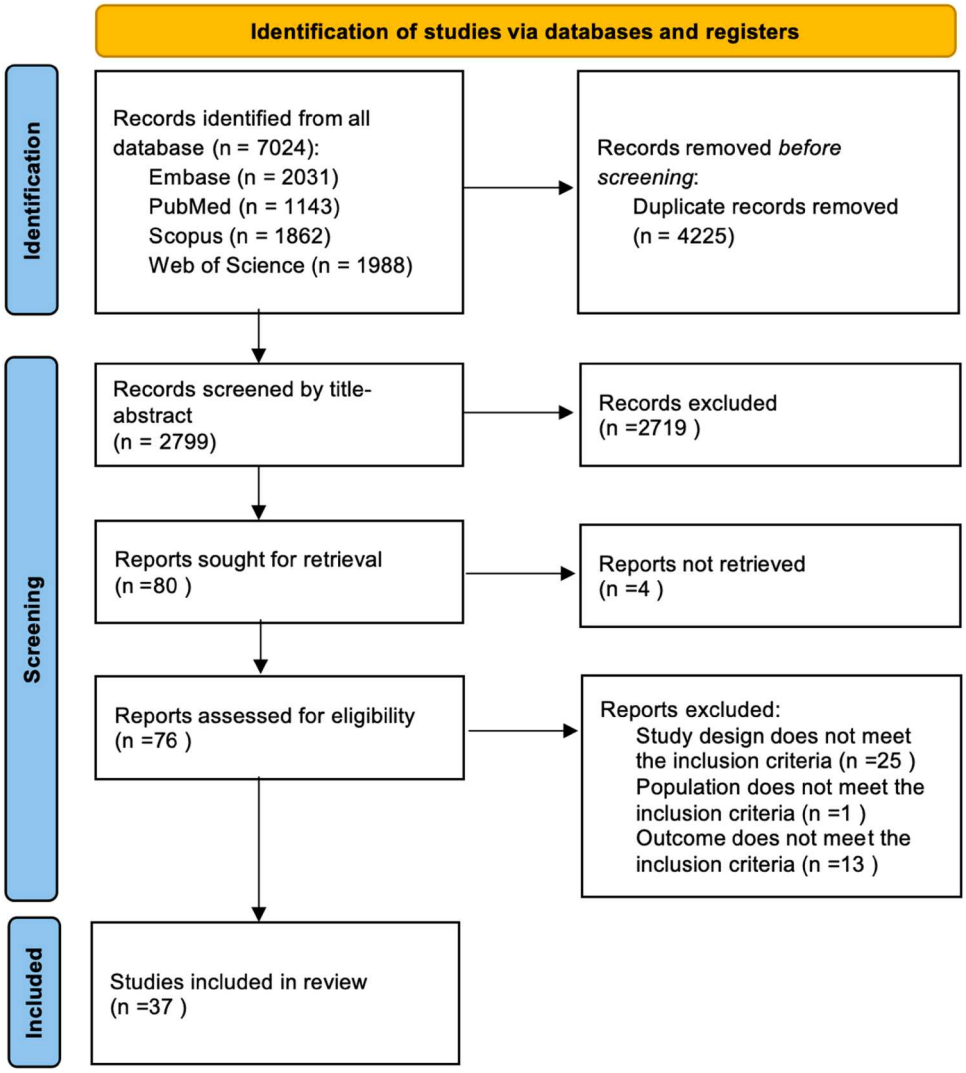

Figure 1. Flow chart illustrating literature search process. *We searched the database until 10 March, 2024.

[29,32] with a sample size of <500 showed a 69% (RR: 0.31, 95% CI: 0.10–0.99) reduction in the incidence of MPXV infection due to vaccination, four studies [19,25,28,31] with a sample size of 500–1,000 showed a 19% (RR: 0.81, 95% CI: 0.40–1.67) reduction in the incidence of MPXV infection, and five studies [20,24,26,27,30] with a sample size of >1,000 showed a 67% (RR: 0.33, 95% CI: 0.17–0.63) reduction in the risk of infection. However, in terms of effectiveness, the subgroup studies revealed no significant differences between the groups.

Protection

Seven studies evaluated the clinical symptoms of mpox and classified them as mild or severe groups. Smallpox vaccine reduced the risk of severe disease in mpox by 39% (RR: 0.61, 95% CI: 0.42–0.87; Figure 3A) [29,33–38]. In addition, when comparing the incidence of mild and severe cases in the same population, we found that smallpox vaccine increased the incidence of mild cases by 11% (RR: 1.11, 95% CI: 1.02–1.21; Figure 3B) [29,33–38], but decreased the incidence of severe cases. One study addressed the impact of vaccines on people living with HIV. The researchers found that HIV-positive mpox participants who received one dose of the JYNNEOS vaccine were 0.28-fold more likely to be hospitalized than HIV-positive participants with mpox who did not receive the vaccination; however, no hospitalizations were reported among HIV-positive individuals with mpox who received a two-dose of JYNNEOS vaccine [36].

For vaccine protection, we performed subgroup analyses according to vaccine type, study region, vaccine dose, and sample size. Smallpox vaccine reduced the risk of severe disease by 64% (RR: 0.36, 95% CI: 0.23–0.56) in North America [34,36,38] and by 26% (RR: 0.74, 95% CI: 0.61–0.90) in Europe [29,33,37] (Figure 4A). Significant differences were observed after grouping by region. When grouped by dose, the incidence of severe disease was reduced by 29% (RR: 0.71, 95% CI: 0.55–0.92) with one dose [29,33–35,37,38] of vaccine, whereas full administration of two doses [36] reduced the incidence by 79% (RR: 0.21, 95% CI: 0.03–1.47; Figure 4B). For different

Table 1. Characteristics of included studies.

Author, Published year	Research design	Duration of study	Country	Population	Age	Gender	HIV positive[a]	Vaccine	Dose	Injection protocol	Sample size	Outcome
Wolff Sagy, Yael et al. [24]	Retrospective cohort	2022.7.31–2022.12.25	Israel	High-risk male	Mean(s.d.) 33.8(5.4)	100% male	647	MVA-BN; Third generation	1	0.5 mL subcutaneous injection	2054	Effectiveness
Rosenberg, Eli S et al. [25]	Case-control study	2022.7.24–2022.10.3	United States	High-risk male & Mpox	Mean(range) 31.3(19.4–74.3); 32.1(18.5–66.4)	100% male	NR	JYNNEOS; Third generation	1 or 2	NR	507	Effectiveness
Ramchandani, Meena S et al. [26]	Retrospective cohort	2020.1.1–2022.12.31	United States	MSM	Median 34	100% male	630	MVA-BN; Third generation	1 or 2	0.5 mL subcutaneous injection; 0.1 mL intradermal injection	4230	Effectiveness
Christine Navarroet et al. [27]	Prospective cohort	2022.6.12–2022.11.26	Canada	High-risk male	Median(IQR) 35(29–46)	100% male	1394	MVA-BN; Third generation	1	NR	6408	Effectiveness
Rosen, Jennifer B et al. [28]	Retrospective cohort	2022.5.22–2022.8.24	United States	Close contact	Mean(range) 35(18–87)	454 male; 101 female	NR	JYNNEOS; Third generation	1	0.1 mL intradermal injection	594	Effectiveness
Hens, Matilde et al. [29]	Prospective cohort	2022.5.23–2022.9.20	Belgium	Suspected case & Mpox	Median(IQR) 37(31–44); 39(33–46)	NR	NR	NR	NR	NR	141	Effectiveness; Protection
Fontán-Vela, Mario et al. [30]	Retrospective cohort	2022.7.21–2022.12.12	Spain	High-risk male	Median(IQR) 36(31–43)	100% male	NR	JYNNEOS; Third generation	1	0.5 mL subcutaneous injection; 0.1 mL intradermal injection	10094	Effectiveness
Deputy, Nicholas P et al. [20]	Case-control study	2022.8.15–2022.11.19	United States	High-risk male & Male Mpox	18–49	100% male	NR	JYNNEOS; Third generation	1 or 2	0.5 mL subcutaneous injection; 0.1 mL intradermal injection	7369	Effectiveness
Dalton, Alexandra F et al. [19]	Case-control study	2022.8.19–2023.3.31	United States	High risk group & Mpox	18–49	834 male; 19 female	265	JYNNEOS; Third generation	1 or 2	0.5 mL subcutaneous injection; 0.1 mL intradermal injection	917	Effectiveness
Brousseau, Nicholas et al. [31]	Case-control study	2022.6.19–2022.9.14	Canada	Male & Male Mpox	≥18	NR	93	MVA-BN; Third generation	1	NR	532	Effectiveness
Montero Morales, Laura et al. [32]	Prospective cohort	2022.5.17–2022.8.15	Spain	Close contact	Median(IQR) 35(31–40); 34 (30–38)	377 male; 114 female	74	JYNNEOS; Third generation	1	0.5 mL subcutaneous injection	484	Effectiveness
van Ewijk, Catharina E et al. [33]	Retrospective cohort	2022.5.20–2022.8.8	Netherlands	Mpox	Median(IQR) 37(31–45)	NR	NR	NR; First generation	NR	NR	208	Protection
Karem, Kevin L et al. [34]	Case-control study	1 years	United States	Close contact & Mpox	NR	13 male; 17 female	NR	NR	NR	NR	29	Protection
Kalthan, E et al. [35]	Cross-sectional study	2016.8–2016.10	Central African Countries	Mpox	Mean(range) 24(1–58)	NR	NR	NR	NR	NR	24	Protection
Schildhauer, Samuel et al. [36]	Retrospective cohort	2022.5.12–2023.5.18	United States	Mpox	Median(IQR) 35(25–48)	4353 male; 123 female	1878	JYNNEOS; Third generation	1 or 2	NR	4611	Protection

(*Continued*)

Table 1. Continued.

Author, Published year	Research design	Duration of study	Country	Population	Age	Gender	HIV positive[a]	Vaccine	Dose	Injection protocol	Sample size	Outcome
van Ewijk, Catharina E et al. [37]	Cross-sectional study	2022.5.20–2022.8.8	Netherlands	Mpox	Median(IQR) 37(31–45)	NR	NR	NR; First generation	NR	NR	177	Protection
Farrar, Jennifer L et al. [38]	Retrospective cohort	2022.5.22–2022.9.3	United States	Mpox	Mean(Median) 36.9(36); 35.3(34)	NR	NR	JYNNEOS; Third generation	NR	NR	3237	Protection
Tomita, Noriko et al. [39]	Prospective cohort	2022.7–2022.12	Japan	Close contact	median±SD(range) 42±6.5(33–49)	100% male	2	LC16; Third generation	1	NR; Bifurcate needle puncture	6	Safety
Montalti, Marco et al. [40]	Cross-sectional study	2022.10–2022.11	Italy	Vaccinated populations	Mean 36.4±8.7	NR	NR	JYNNEOS; Third generation	1 or 2	0.1 mL intradermal injection	185	Safety
Lee, Jaeeun et al. [41]	Prospective cohort	2022.8–2022.11	South Korea	Occupational exposure risk populations	≥20	42 male; 44 female	NR	JYNNEOS; Third generation	1 or 2	0.5 mL subcutaneous injection	86	Safety
Kennedy, Jeffrey S et al. [42]	Phase I/II clinical trial	2004.10–2005.6	United States	Healthy group	Mean(SD) 23.3(3.9)	97 male; 56 female	NR	LC16m8 & Dryvax; Third & First generation	1	NR; Bifurcate needle puncture	153	Safety; Cross-Immunogenicity
Duffy, Jonathan et al. [43]	Cross-sectional study	2022.5.22–2022.10.21	United States	Vaccinated populations	NR	NR	NR	JYNNEOS; Third generation	1 or 2	0.5 mL subcutaneous injection; 0.1 mL intradermal injection	537	Safety
Deng, Lucy et al. [44]	Cross-sectional study	2022.8.8–2023.3.20	Australia	Vaccinated populations	Median(IQR) 41(33–52)	5639 male; 180 female	NR	MVA-BN; Third generation	1 or 2	0.5 mL subcutaneous injection; 0.1 mL intradermal injection	13306	Safety
Frey, Sharon E et al. [45]	randomized clinical trials	NR	United States	Vaccinated populations	Median(range) 27.1(18–38.2); 26.6(18.1–38.2)	87% male; 89% male	NR	JYNNEOS; Third generation	1 or 2	0.5 mL subcutaneous injection; 0.1 mL intradermal injection	358	Safety
Lim, So Yun et al. [46]	Cross-sectional study	2023.5.22–2023.7.31	South Korea	Vaccinated populations	Median(IQR) 41(34–48)	76 male; 64male	NR	JYNNEOS; Third generation	1 or 2	0.1 mL intradermal injection	142	Safety
Swift, Melanie D et al. [47]	Cross-sectional study	2022.11–2022.12	United States	Vaccinated populations	NR	NR	NR	JYNNEOS; Third generation	1 or 2	0.5 mL subcutaneous injection; 0.1 mL intradermal injection	44	Safety
Mazzotta, Valentina et al. [48]	Prospective cohort	NR	Italy	Occupational exposure risk populations	Median(IQR) 49(41–55)	NR	NR	MVA-BN; Third generation	1	0.5 mL subcutaneous injection; 0.1 mL intradermal injection	111	Safety; Cross-Immunogenicity
Moschetta, Nicolò et al. [49]	Neutralization test	Blood samples were collected 6 months from baseline	Italy	Mpox & Vaccinated populations	Median(IQR) 37.2(32.2–41.8)	100% male	65	MVA-BN; Third generation	NR	NR	180	Cross-Immunogenicity
Raadsen, Matthijs *P* et al. [58]	Neutralization test	58 weeks	Germany	Subjects from previous clinical trial	18–40	NR	NR	MVA-MERS-S; Third generation	3	NR	10	Cross-Immunogenicity
Matusali, Giulia et al. [53]	Neutralization test	NR	Italy	Healthy group	NR	NR	NR	NR	NR	NR	97	Cross-Immunogenicity
Li, Entao et al. [54]	Neutralization test	NR	Italy	Healthy group	19–63	50% male; 50% female	0	VTT; Second generation	NR	NR	294	Cross-Immunogenicity
Zaeck, Luca M et al. [55]	Neutralization test	NR	China	NR	NR	NR	NR	Imvanex; Third generation	NR	NR	238	Cross-Immunogenicity

Sammartino, Josè Camilla et al. [57]	Neutralization test	2022.5–2022.8	Italy	Mpox	Median(range) 36(20–64)	100% male	NR	NR	NR	NR	6	Cross-Immunogenicity
Moschese, Davide et al. [52]	Neutralization test	12 weeks	Italy	Vaccinated populations	Median(IQR) 35(31–40)	100% male	19	JYNNEOS; Third generation	2	0.5 mL subcutaneous injection; 0.1 mL intradermal injection	72	Cross-Immunogenicity
Manenti, Alessandro et al. [56]	Neutralization test	NR	Italy	Mpox & Healthy group	NR	NR	NR	NR	NR	NR	50	Cross-Immunogenicity
Kottkamp, Angelica C et al. [51]	Neutralization test	NR	United States	Vaccinated populations	NR	85% male	24%	MVA-BN; Third generation	2	NR; subcutaneous injection & intradermal injection	145	Cross-Immunogenicity
Asquith, Will et al. [50]	Neutralization test	NR	Australia	Mpox & Vaccinated populations	18–60	30 male; 17 female	NR	MVA-BN; Third generation	2	NR	47	Cross-Immunogenicity

NR, Not Reported.
[a], The number of HIV-Infected individuals in the total sample size included in the study.

types of smallpox vaccine, we found that the first-generation smallpox vaccine [33,37] reduced the incidence of severe disease by 29% (RR: 0.71, 95% CI: 0.60–0.84), while the third-generation smallpox vaccine [36,38] reduced the incidence by 64% (RR: 0.36, 95% CI: 0.22–0.56), with significant differences between groups (Figure 4C). Finally, subgroup analysis of sample size showed that the vaccine reduced the risk of severe disease by 27% (RR: 0.73, 95% CI: 0.59–0.90) in five studies [29,33–35,37] with a sample size of <500, and by 64% (RR: 0.36, 95% CI: 0.22–0.56) in two studies [36,38] with a sample size of >1,000. The differences between groups with different sample sizes were significant (Figure 4D).

Safety

In a pooled analysis of studies evaluating the safety of smallpox vaccine for the prevention of MPXV infection, we found that the incidence was 56.3% (ES: 0.563, 95% CI: 0.425–0.696) for local erythema [39–41,43–48], 55.1% (ES: 0.551, 95% CI: 0.371–0.724) for local swelling [39–41,43,44,46,47], 49.7% (ES: 0.497, 95% CI: 0.104–0.891) for local induration [39,40,45,48], 47.8% (ES: 0.478, 95% CI: 0.270–0.690) for local itching [40,43,44,46,47], and 39.2% (ES: 0.392, 95% CI: 0.242–0.552) for local pain [39–44,46–48] after vaccination (Figure 5). In addition, the incidence of vomiting [40,46,48], shivering [40,44,46–48], and having headache [39–41,43,44,46–48], rash [39,42,43,47], myalgia [40,41,44,46,48], and fatigue [40,41,43,44,46–48] ranged from 0.9% to 19% (Figure S6 in Multimedia Appendix 4). Specific information regarding safety outcomes is provided in Multimedia Appendix 5.

Cross-Immunogenicity

Several studies have shown that anti-MPXV neutralizing antibodies (nAbs) and anti-MPXV immunoglobulin G (IgG) can be detected in the serum of participants who received the smallpox vaccine. Moschetta et al. [49] used the plaque reduction neutralization test to establish anti-MPXV nAbs titres 6 months after the first vaccination. The results showed that among people who received the Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) vaccination, the most common antibody titre was 1/10 (29 [34%]), and some people (10 [12%]) had no detectable antibodies in their samples (<1/10). Asquith et al. [50] reported that 83% of the vaccine recipients exhibited MPXV antibodies 14 days after vaccination. Another study reported a serum geometric mean titre (GMT) of 112 (95% CI: 82–307) 30 days after vaccination with the attenuated smallpox vaccine LC16m8 [42]. Mazzotta et al. [48] also showed that the level of both anti-MPXV IgG and anti-MPXV nAbs increased

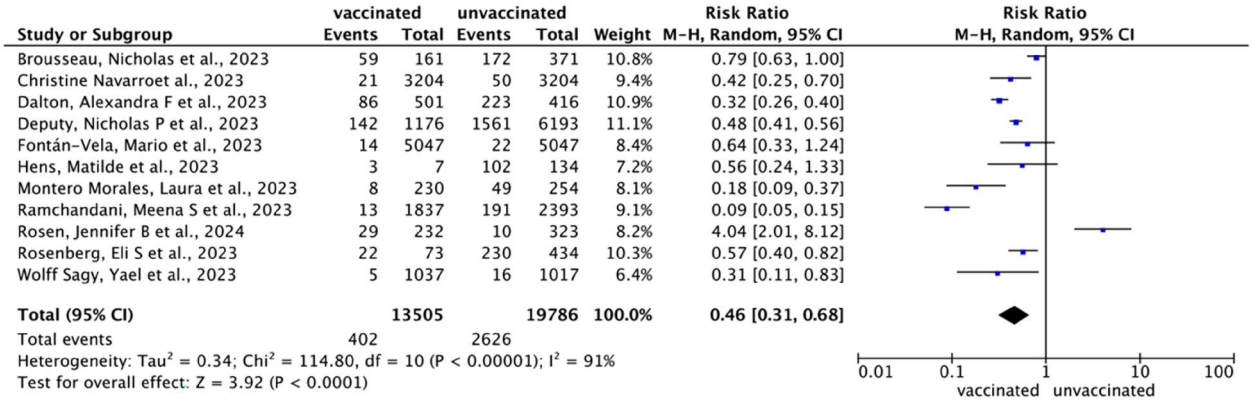

Figure 2. Meta-analyses on effectiveness profiles of vaccinated and unvaccinated.

significantly after MVA-BN administration. Kottkamp et al. found that the GMT was four-fold higher after two doses than after one dose (199.4 vs 49.6) among participants without previous smallpox vaccination [51]. However, lower nAb titres were induced after JYNNEOS vaccination compared with that with MPXV infection [52]. While many studies have found that smallpox vaccines administered in the late twentieth century may still confer a certain protection, Matusali et al. discovered that, among a group of people vaccinated against smallpox in the past, 60 (89.6%) had detectable levels of anti-MPXV IgG

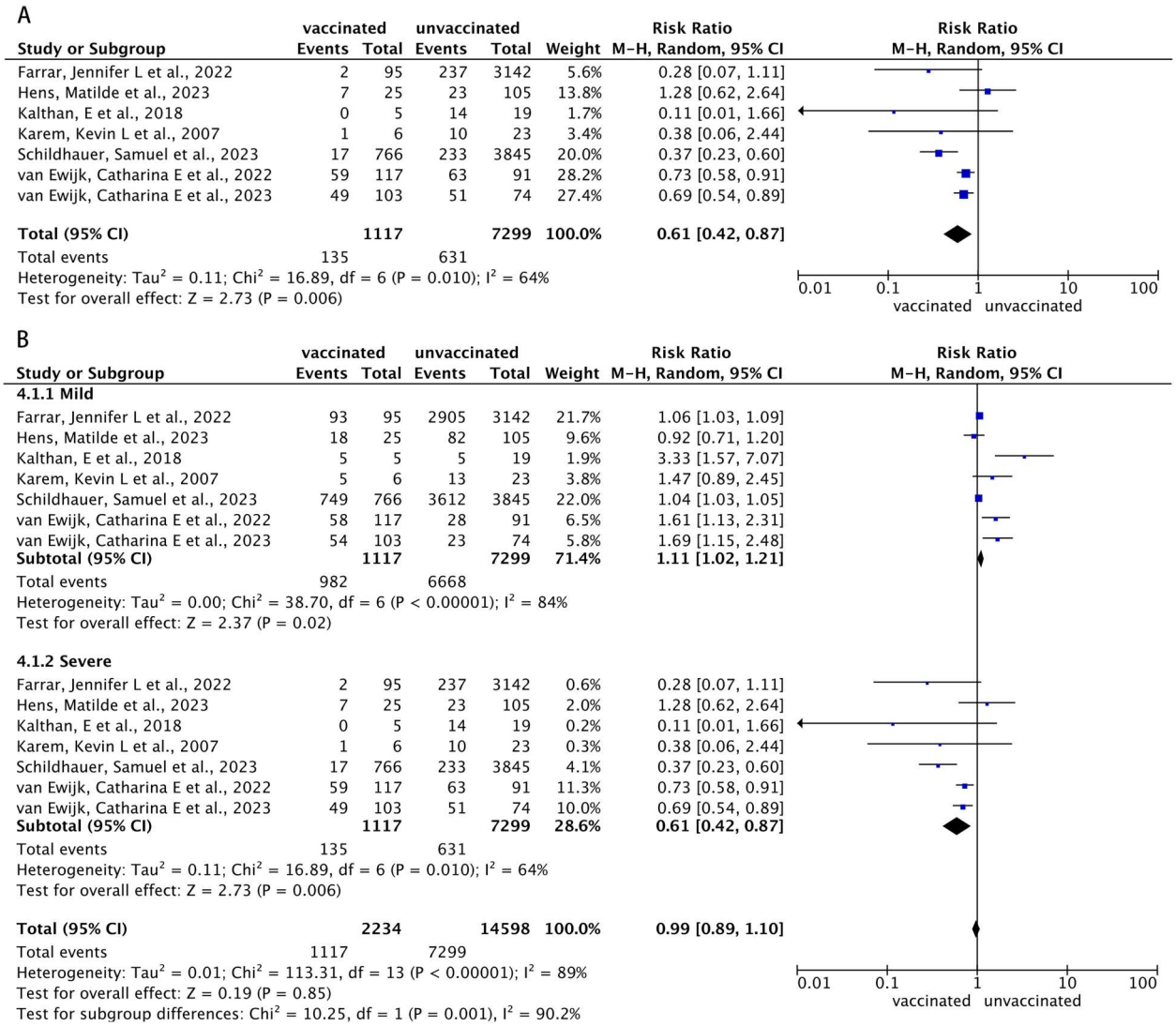

Figure 3. Meta-analyses on protection profiles of vaccinated and unvaccinated. (A) The effect of vaccination on severe disease. (B) The effect of vaccination on mild and severe disease.

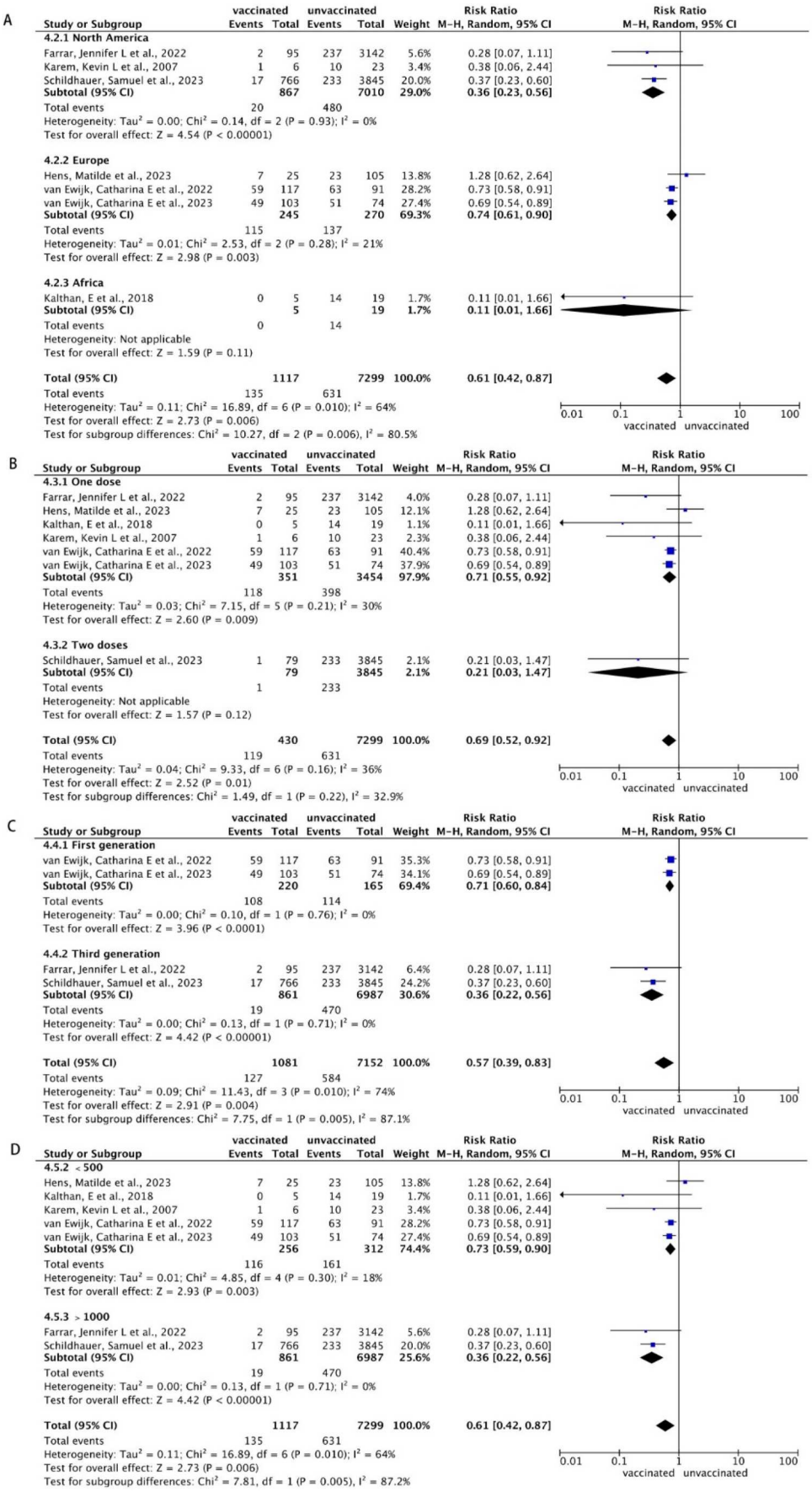

Figure 4. Subgroup analyses on protection profiles of vaccinated and unvaccinated. (A) Subgroup analysis by region. (B) Subgroup analysis by dose. (C) Subgroup analysis by vaccine generation. (D) Subgroup analysis by sample size.

while 40 individuals (70.1%) possessed nAbs. The GMT was 75.2 (95% CI: 56.7–99.7) for IgG and 17.5 (95% CI: 13.4–22.8) for nAbs [53]. A study in China showed that antibodies against the MPXV surface antigen A35/B6R were detectable in the plasma of 84.91% of participants aged 54–63 years [54]. A study in the Netherlands also detected MPXV neutralization only in the sera of participants born before 1974 (n = 19) [55]. Similar results were reported by Manenti et al. [56]. However, among the 23 participants included in the study by Moschese et al. [57], a 1:5 titre of MPXV-specific IgG was detected in 11 (48%) participants, although nAbs were undetectable. The MVA MERS-S is an MVA vector-based vaccine candidate against Middle East respiratory syndrome (MERS)-associated coronavirus. Researchers tested anti-MPXV nAbs in a group of participants vaccinated with MVA-MERS-S and found that the positive rate of nAb detection increased with the vaccination doses. The positive rate was 100% (10/10) and the GMT was 107 (95% CI: 36–323) after three doses of vaccination [58].

Discussion

Principal findings

This is an updated and comprehensive meta-analysis on the use of smallpox vaccine as an emergency prevention tool for the spread of mpox in the real world. Our results showed the following: (1) Smallpox vaccination effectively protected against MPXV infection in high-risk populations, and the impact of the vaccine dose on effectiveness was not significant. (2) Smallpox vaccination significantly reduced the incidence of severe mpox, and the protection conferred by the third-generation smallpox vaccine was better than that conferred by the first-generation. (3) People living with HIV should be prioritized for smallpox vaccination to reduce the risk of MPXV infection and severe disease. (4) Smallpox vaccination is safe. Adverse reactions, such as local erythema, swelling, induration, itching, and pain, were common after smallpox vaccination; however, these symptoms were mild and disappeared in a short period of time, without causing any serious influence on the health of the participants. (5) The mpox nAbs detected in the vaccinated participants confirmed that the smallpox vaccine could induce cross-protection against mpox.

Previously published studies on smallpox vaccines have revealed that people who have been previously vaccinated against smallpox have higher immunity and fewer serious adverse events after vaccination than those receiving the first smallpox vaccine [59]. Subsequent research revealed no notable differences in the negative consequences between the MVA vaccine and a placebo, and seroconversion rates were higher with two doses than with one dose [60]. However, one of the above two studies focused on the safety and efficacy of the vaccine, and the other focused on the safety and immunogenicity, lacked a summary of the protection. Therefore, it is impossible to make a full assessment of the effect of smallpox vaccine. In addition, the articles included in these two studies were published at an early age, which has little significance in guiding the current monkeypox epidemic. Another study similar to ours reported that early smallpox vaccine immunization demonstrated a degree of protection against monkeypox [61]. However, neither the assessment indicators nor the study regions are comprehensive enough in their study, so the findings may not be broadly representative. Based on the aforementioned studies, we focused on the cohort studies conducted after a major outbreak of mpox in 2022, supplemented the relevant evidence on the effectiveness and protection of the smallpox vaccine in preventing mpox infection, and extracted more detailed data on the adverse reactions caused by the smallpox vaccine for further evaluation of its safety. Finally, we systematically summarized the recent progress in the cross-immune response of the the smallpox vaccine to MPXV. Notably, we included multiple studies in the Americas, Africa, Asia, Europe and Oceania, which makes the findings globally representative. Therefore, our study provides a more detailed and comprehensive assessment of the effect of smallpox vaccination on mpox infections.

A systematic review by Xu et al. [62] also reached a conclusion similar to our study that widespread vaccination with the MVA-BN vaccine (third-generation) effectively prevents MPXV infection. By integrating data from studies of third-generation smallpox vaccines for the prevention of mpox, we found that the new-generation smallpox vaccine significantly reduced the prevalence of mpox among MSM and close contacts who were at a high risk of mpox infection. In addition, we studied the protection conferred by the new-generation smallpox vaccine and found that this was superior to the previous smallpox vaccine in terms of protection by significantly reducing the incidence of severe mpox. Nevertheless, the third-generation smallpox vaccine, which is a highly attenuated virus with replication ability, is very safe [63,64], but its immunogenicity in humans is lower than that of first-generation vaccines [65]. Hence, the findings of our investigation differ from those of previous studies. We speculate that although first-generation smallpox vaccines played a major role in the eradication of the disease in the late twentieth century, the protection conferred by the original smallpox vaccine appears to wane over time [66]. Since the mpox outbreak, several cases have been reported in individuals vaccinated against smallpox [67]. Data on the residual protection of childhood smallpox vaccine are lacking; however,

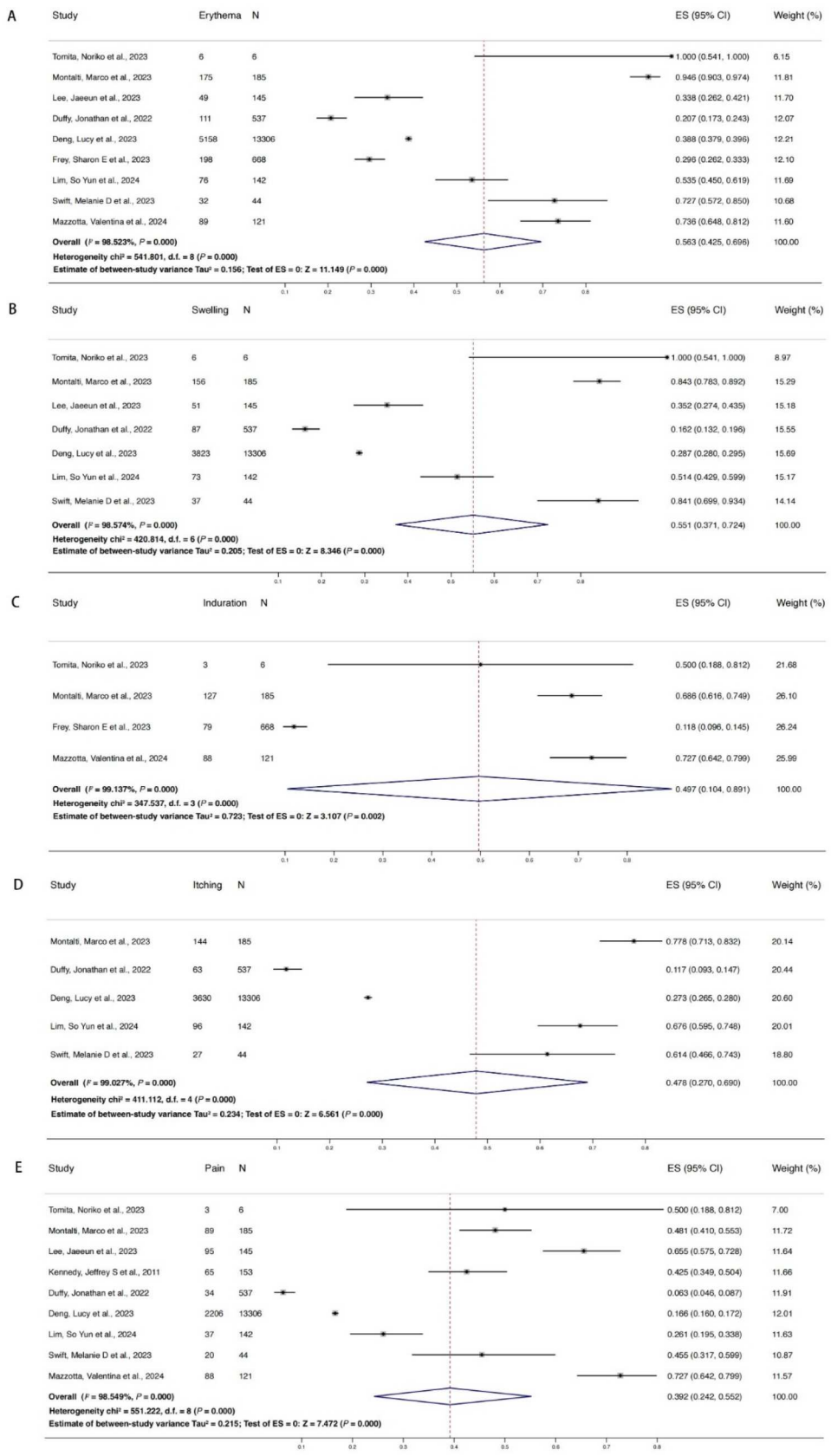

Figure 5. Meta-analyses on safety of vaccinated. (A) Local erythema after vaccination. (B) Local swelling after vaccination. (C) Local induration after vaccination. (D) Local itching after vaccination. (E) Local pain after vaccination.

our study proved that the third-generation smallpox vaccine provides significantly better protection than the historic first-generation smallpox vaccine, compensating for the deficiency of research. Therefore, our results suggest that regardless of smallpox vaccination in children, supplemental vaccination with new-generation smallpox or mpox vaccines is necessary to address existing mpox outbreaks.

Moreover, we conducted an in-depth analysis of the dose data for the third-generation smallpox vaccines. Our data revealed a 39% reduction in the incidence of MPXV infection after one dose and an 82% reduction after two doses of the vaccine. Similarly, the two doses were more protective than a single dose in reducing clinical symptoms, although no notable differences were detected between the regimens that involved the administration of one or two doses. This may help advocate the the administration of a single dose of smallpox vaccine in the context of insufficient stock. However, recent research on the 2022 US mpox outbreak determined that the JYNNEOS vaccine had an estimated efficacy of 35%–75% after one dose and 66%–85% after two doses in preventing mpox [19,20]. The reason our results differed from those of previous studies may be that the number of articles in our included studies was small and heterogeneous. Therefore, to ensure the rational use of limited vaccine resources, a single dose of vaccine is recommended for high-risk groups if the vaccine stockpile is insufficient. However, further research is required to assess the impact of vaccine doses on the prevention of mpox and disease symptoms.

Additionally, we confirmed the protective effects of the third-generation vaccines in the high-risk populations. Since the 2022 mpox outbreak, 10.9% of the patients with available data required hospitalization, 0.3% required intensive care, and 0.3% died [8]. Several studies have shown that HIV infection is a high risk factor for hospitalization, severe illness, and death in patients with mpox [68,69]. Therefore, as a high-risk group for severe and fatal mpox, people living with HIV require more attention. Mpox causes significantly more severe illnesses and longer-lasting illnesses in patients with advanced or untreated HIV infection [70–72]. An analysis of 57 patients admitted to a hospital with severe mpox in the US revealed that 82% were diagnosed with HIV infection. Among these individuals, nearly 75% have a CD4 count of <50 cells per mm^3 [73]. Preventive methods and clinical treatment drugs are urgently required to manage such conditions. We found that smallpox vaccination effectively reduced the risk of severe mpox. A study by Schildhauer et al. [36] showed that HIV infection had no effect on the response to the smallpox vaccine and that smallpox vaccination reduced hospitalization rates among HIV-positive patients with mpox. Therefore, smallpox vaccination for HIV-infected populations should be prioritized. However, evidence from a single study is insufficient, and further research is needed on the prevention and control strategies for mpox in HIV-infected populations.

By analysing the adverse reactions caused by the third-generation smallpox vaccine, we found that most adverse reactions caused by the third-generation smallpox vaccine were mild local symptoms, such as local erythema, swelling, induration, itching, and pain. Other studies have also mentioned that common side effects of the JYNNEOS vaccine include redness or irritation at the site of injection, fatigue, headache, and body aches [21]. However, even without treatment, these symptoms tend to disappear after 1 to 3 days [45], with minimal non-life-threatening effects on the patients. This indicates that the results of our study are consistent with the findings of previous studies reporting the safety of the smallpox vaccine.

Neutralizing antibodies prevent pathogens from binding to host cell surface receptors, thereby preventing them from adhering to and invading target cells to replicate and reproduce [74]. Therefore, nAb levels are important indicators of host immunity. We observed that the smallpox vaccine induced cross-protection against mpox. Both the first- and third-generation smallpox vaccines, and other vaccines using poxviruses as vectors, can induce the production of anti-MPXV IgG and anti-MPXV nAbs. Successful induction of anti-MPXV nAbs by the smallpox vaccine confirmed that this confers cross-protection against mpox. However, another study has found a considerable loss (>6-fold reduction) in the efficiency of MPXV-nAb elicitation with the vaccinia virus Tiantan strain. These findings indicated that VACV is a more appropriate option for use as a smallpox vaccine than the mpox vaccine [75]. Therefore, further research is required to investigate the extent to which various smallpox vaccines offer cross-protection against mpox, and the development of specific vaccines against mpox is necessary.

Limitations

Our study had several limitations. First, because of the small number of included studies and the fact that many characteristics could not be integrated into analysis, a high heterogeneity of unknown sources was observed in our articles. Second, to assess the protective effect of the smallpox vaccine against monkeypox, we included measures of cross-immunogenicity rather than the immunogenicity of the smallpox vaccine itself. In addition, owing to the diverse presentation formats of the cross-immunogenicity results, data could not be combined for meta-analysis. Third, to date, the smallpox vaccine has only been used as a preventive measure against mpox infection in Europe and America. The key reasons for the lack of research data in other regions are insufficient smallpox vaccine reserves and unsupportive policies. Finally, we selected and retained only primary research while excluding conferences and the corresponding data. This may have resulted in the exclusion of accurate data and diminished the effectiveness of the findings.

Conclusions

Our findings show that smallpox vaccine is safe and effective against monkeypox worldwide, and the protection of the third-generation smallpox vaccine may not be affected by the doses given. Notably, smallpox vaccine shows an obvious advantage in high-risk populations such as MSM and HIV-infected people as well. It is recommended that one dose of the third-generation smallpox vaccine should be provided as a priority for high-risk groups, especially those infected with HIV. However, owing to the shortage of vaccine stocks, more studies are urgently needed to compare the prevention and treatment effects of different doses to ensure that the limited vaccine can be more rationally distributed. Furthermore, considering the reduced immune response to previous smallpox vaccination, the occurrence of breakthrough infections, and the potential variation of the virus, developing a new generation of more effective and specific mpox vaccines is recommended to deal with the current mpox outbreak.

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Disclosure statement

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

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Data availability statement

All data generated or analyzed in this study are publicly available and are included in this published article.

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