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RE-EMERGING OUTBREAK, SMALLPOX VACCINATION FOR MONKEYPOX INFECTION: A SYSTEMATIC REVIEW

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ABSTRACT
Monkeypox disease is caused by the monkeypox virus (MPXV) infection and is associated with international travel or imported animals. Since May 2022, the number of newly reported cases each week has increased dramatically, leading the WHO to declare this outbreak as a public health emergency of international concern. To evaluate antibody response and disease status after monkeypox vaccination using the smallpox vaccine. The authors followed the PRISMA guidelines to systematically search and collect literature from the following databases: ProQuest, PubMed, EBSCOhost, SAGE, Taylor & Francis, and GARUDA without time restrictions. Titles and abstracts were reviewed for relevance. The inclusion criteria were original articles written in English that investigated the effects of smallpox vaccination on MPXV infection. A total of 973 studies were initially identified through database searching. After removing duplicates and screening titles and abstracts based on the predefined inclusion and exclusion criteria, potentially relevant articles were assessed through full-text review. Following this eligibility assessment, 30 studies were included in the final analysis. These included cohort studies (n=1), case-control studies (n=1), case reports (n=1), and in vivo studies (n=27) published between 2002 and 2022. Two types of smallpox vaccines were used: live attenuated vaccines (n=24) and subunit vaccines made from protein (n=1), virus-like replicon particles (n=1), and DNA virus (n=5). The overall results showed that post-exposure vaccination protected subjects and could induce long-term protection against severe MPXV infection. Subunit vaccines against MPXV could also serve as a safer alternative to live attenuated vaccines. Smallpox vaccination is recommended for high-risk groups susceptible to monkeypox infection. Specific vaccines for monkeypox infection are still being developed. This systematic review found that the overall potential of smallpox vaccines is quite satisfactory in preventing MPXV infection.

Keywords: antibody response; monkeypox; smallpox; vaccine

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INTRODUCTION

Monkeypox is an infectious disease caused by the monkeypox virus (MPXV). This virus belongs to the Orthopoxvirus genus, a double-stranded DNA virus enveloped in the Poxviridae family. The virus is transmitted through zoonosis, meaning it is transmitted from animals to humans. It can also be transmitted through direct contact with wounds, body fluids, and shared use of contaminated items. Cases of monkeypox in Indonesia have also been reported in August 2022, affecting a 27-year-old male with a history of travel to several countries. Globally, the number of monkeypox cases has reached 79,231. In Africa, from 1970 to September 2022, there have been 57,995 cases of monkeypox. Since May 2022, the number of newly reported cases each week has dramatically increased, leading the WHO to declare this outbreak as a public health emergency of international concern (Huang et al., 2022; Rao et al., 2022). Currently, there is no specific management for monkeypox, but it can be prevented through smallpox vaccination. There are two types of monkeypox vaccines: JYNNEOS and ACAM2000. JYNNEOS is a vaccine that contains a live virus produced from the modified Ankara Bavarian Nordic (MVA-BN strain) and weakened orthopoxvirus that does not replicate. The indication for administering JYNNEOS vaccine is

individuals aged ≥18 years with a high risk of infection. ACAM2000 vaccine contains live vaccinia virus and is indicated for high-risk groups for monkeypox infection. The difference between the two vaccines lies in the cutaneous reactions they induce. With the ACAM2000 vaccine, cutaneous reactions occur at the inoculation site, while JYNNEOS vaccine does not cause cutaneous reactions (Rao et al., 2022). The reemergence of virus transmission after many years necessitates the development of strategies, including vaccination, to prevent infection. Currently, there is no research that examines and evaluates antibody response and disease status against monkeypox infection after smallpox vaccination. This systematic review aims to assess the potential of smallpox vaccine as a preventive measure against monkeypox infection.

METHOD

This systematic review followed the Preferred Reporting Items guidelines for Systematic Reviews and Meta-analyses (PRISMA).

Literature Search

The authors conducted a comprehensive literature search to find out the immunogeneity of smallpox vaccination against monkeypox infection and its side effects through the search sites ProQuest, PubMed, EBSCOhost, SAGE, and Taylor&Francis. Article retrieved without time inception. The search terms applied on PubMed were as follows : (((((((((("immunology"[MeSH Subheading]) OR ("Immunity, Heterologous"[Mesh])) OR ("Immunity, Humoral"[Mesh])) OR ("Adaptive Immunity"[Mesh])) OR ("Immunity, Active"[Mesh])) OR (immune response)) OR (immunity)) AND ((Disease status) OR (Severity))) AND ((("monkeypox vaccines"[Mesh]) OR (monkeypox vaccine)) OR (monkeypox vaccination))) AND (("monkeypox"[Mesh]) OR (monkeypox)). The literature search was limited to full text studies published in English.

Study Selection

The inclusion criteria used were as follows: (1) Original article; (2) Written in English; (3) Availability of full text (fulltext); (4) Report the effect of smallpox vaccine on monkeypox infection. The exclusion criteria used was lack of data availability (the outcome assessment, measurement method and measuring instrument).

Data Extraction

Six authors extracted further information independently about the included studies, and the fifth author resolved any differences that existed among the other authors. The extracted data for clinical studies were as follows: (1) Author and publication year; (2) Study design; (3) Methods (vaccine type; subjects; virus challenge); (4) Outcome (antibody titers, virus level, and clinical manifestation)

Outcome Assessment

The outcome assessment in this study was divided into three categories: antibody titers, virus level, and clinical manifestation. These outcomes were assessed after administering the vaccine and exposing the subjects to MPXV challenge.

Quality Assessment

The risk of bias assessment was carried out by four authors. Some of the quality assessment tools used include: Joanna Briggs Institute (for studies using case report, case series, and cross-sectional), Critical Apprasial Skills Programme (for case control), Newcastle-Ottawa Scale (for cohort), and SYRCLE risk of bias (for in vivo studies).

Ethical Approval

None of the writers of the articles included in this systematic review conducted any research on people or animals. Each study followed the ethical guidelines outlined in the relevant articles. As stated in the individual articles, patient informed consent was obtained for all research.

RESULT

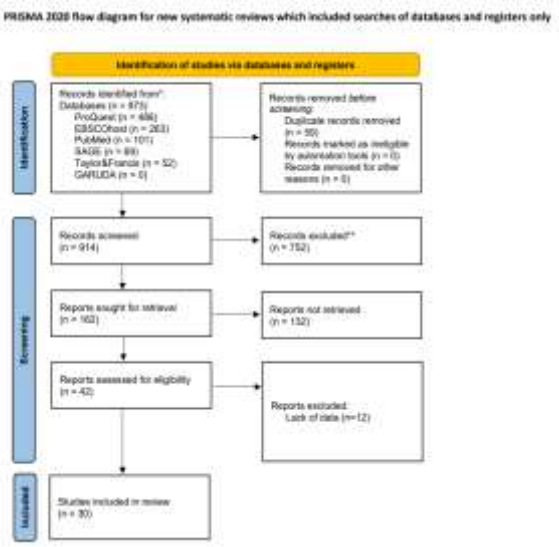


Figure 1. PRISMA flowchart 2020

The studies used in this systematic review were published in English from 2002 to 2022 (Figure 1). Included studies consisted of cohort studies (n=1), case-control studies (n=1), case reports (n=1), and in vivo studies (n=27). A total of 973 articles were retrieved during the initial search. After excluding duplicate articles, 914 potential articles were selected for title and abstract screening. Articles with lack of data availability were excluded. After title and abstract screening, 162 articles were included for full-text assessment, and it was found that 30 articles were used in this systematic review.



Figure 2. The Joanna Briggs Institute Risk of Bias



Figure 3. The Critical Appraisal Skills Programme (CASP) risk of bias

Overall, the risk of bias assessment using various tools showed low to high risk of bias. The risk of bias assessment using Joanna Briggs Institute (for studies using case report, case series, and cross-sectional) showed low risk of bias (Figure 2). Critical Apprasial Skills Programme (for case

control) tools showed low to moderate risk of bias (Figure 3). The Newcastle-Ottawa Scale (for cohort studies) showed high quality studies (Table 1). Meanwhile, the SYRCLE risk of bias (for in vivo studies) showed relatively high risk of bias (Figure 3).

Table 1.
The Newcastle-Ottawa Scale Risk of Bias

	selection				compararability		outcome		Total score (max 9)
Author	Representative of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at star of study	Comparability of cohort on the basis of the design or analysis	Assesment of outcome	Was follow-up long enough for outcomes to occur	Adequancy of follow up cohorts	
Zaeck et al (2022)	1	0	1	1	2	0	1	1	7 (high quality)

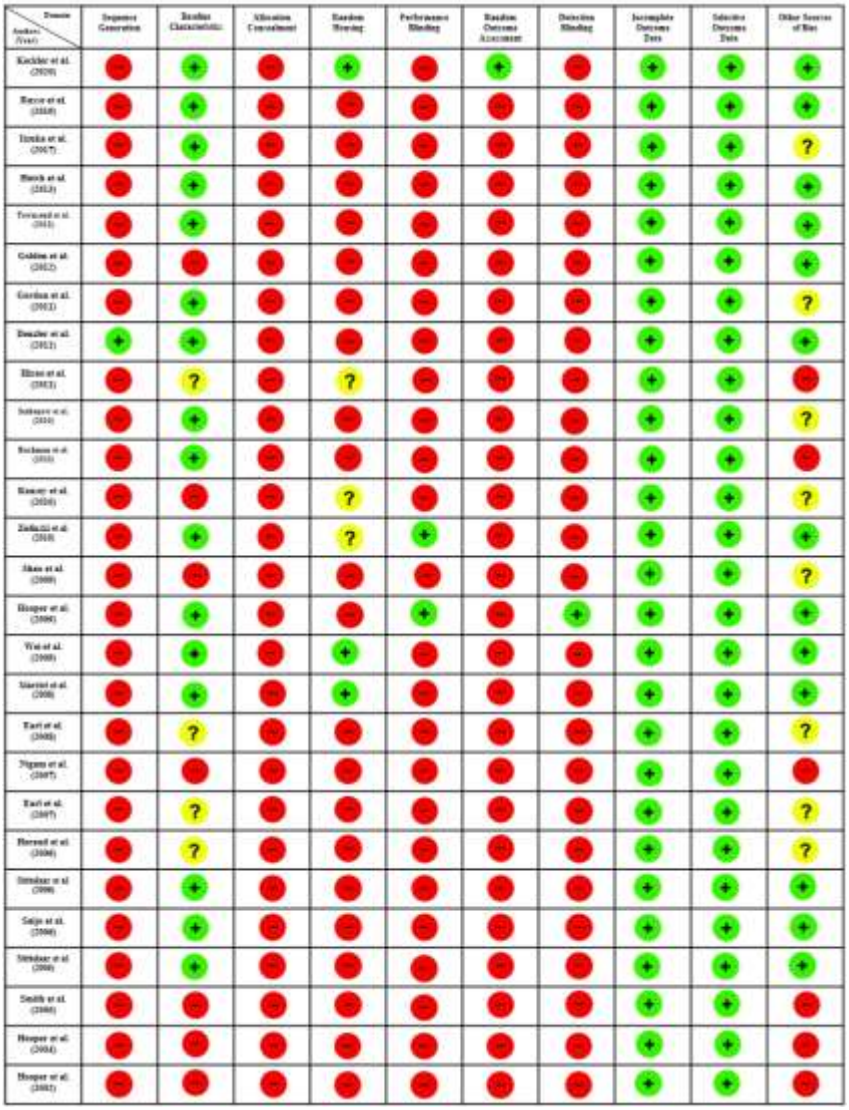


Figure 3. SYRCLE Risk of Bias

Two types of smallpox vaccines were used (Table 2): live attenuated vaccines (n=24) and subunit vaccines made from protein (n=1), virus-like replicon particles (n=1), and DNA virus (n=5). The overall results showed that post-exposure vaccination protected subjects and could induce long-term protection against severe MPXV infection. In terms of critical appraisal results, the quality of case reports, case-control studies, and cohort studies yielded satisfactory results. However, for in vivo studies, there were components that were not clearly mentioned in the studies we collected.

Additionally, almost all studies did not perform sequence generation, allocation concealment, random housing, performance blinding, or detection blinding.

Table 2.
Smallpox vaccination against MPXV

Author (Year)	Study Design	Methods			Outcome		
		Vaccine	Subject	Viruses	Antibody Titer	Viruses Level	Clinical Manifestation
(Zaeck et al., 2023)	Cohort	Modified vaccinia virus Ankara-Bavarian Nordic (MVABN, also known as Imvamune, Jynneos, or Imvanex)	Human (n=238) Serum samples were divided into four different cohorts: an age panel cohort; diagnostic cohort; Imvanex cohort; and MVA-H5 cohort.	N/A	MPXV-neutralizing antibodies can be detected following MPXV infection and smallpox vaccination. However, 2 injections of MVA-BN immunization in non-prime individuals result in a low level of MPXV-neutralizing antibodies.	N/A	N/A
(Turner et al., 2022)	Case report	ACAM2000 smallpox	Human The patient in United States was a previously healthy 34-year-old man who had sex with men came to a walk-in sexually transmitted infections clinic because of a 4-day history of malaise, fatigue, and headache and a 2-day history of 4 painless penile lesions.	N/A	N/A	N/A	A patient who had been vaccinated with ACAM2000 eight years prior, still contracted the disease. The patient exhibited prodromal symptoms before the development of painless penile lesions.
(Keckler et al., 2020)	In vivo	IMVAMUNE® ACAM2000®	Prairie dog Unvaccinated (n = 4), ACAM2000® day 1 (n = 8), ACAM2000® day 3 (n = 8), IMVAMUNE® day 1 (n = 8), and IMVAMUNE® day 3 (n = 8)	10^4 pfu MPXV (2× LD50)/10^6 pfu (170× LD50)	Day 0: All groups had antibody titers below the level of detection. Day 7: Small increase in all group titers. ACAM2000® group showed a log increase that was not seen in IMVAMUNE® group or unvaccinated group(2× LD_{50} dose) and was not seen in any groups (170× LD_{50} dose). Day 0-14: Titers rising significantly (p < 0.05).	Oral swabs: All vaccinated groups had decreased viral DNA on Day 14, with only ACAM2000® group produced a significantly lower median peak viral DNA. IMVAMUNE® group showed lower median peak viral DNA compared to control group. In blood test: Dryvax® group resulted in significantly lower median peak viral DNA	The time to death was delayed in a subset of PEP-vaccinated animals. Mortality rates: The lowest was 12% (1/8) with IMVAMUNE® (day 1 postexposure). For other treatments, 62% (5/8) IMVAMUNE® (day 3), 50% (4/8) with ACAM2000® (day 1), and 38% (3/8) with ACAM2000® (day 3). Inappetence (at the 2× LD_{50} dose) onset: Day 1 or 2: All

Author (Year)	Study Design	Methods			Outcome		
		Vaccine	Subject	Viruses	Antibody Titer	Viruses Level	Clinical Manifestation
						in blood when compared to control group. IMVAMUNE® group had a lower median peak viral DNA compared to control group.	other groups Day 6: ACAM2000® vaccinated on day 3 Day 7: Unvaccinated group Weight loss onset: Day 9 to 10: Vaccinated group Day 13: Unvaccinated group Lesions onset: Day 6: Unvaccinated group Day 9 or 10: Vaccinated group Day 14: Vaccinated one day postexposure with IMVAMUNE® group
(Russo et al., 2020)	In vivo	ACAM2000	Study 1 (*Cynomolgus monkeys*): Female (n=8); male (n=8) from NIH Animal Center (Poolesville, MD). Study 2 (*Cynomolgus monkeys*): Female (n=3); male (n=3) from Covance Research Products (Princeton, NJ). Study 3 (Indian rhesus macaques): Female (n=3); male (n=3) from Primate Products, Inc. (Immokalee, FL).	MPXV Zaire 79 strain V79-I-005 ($1.65x10^7$ and $5.4x10^7$ p.f.u.)	The vaccinated group showed a superior primary immune response compared to the control group. Peak geometric mean neutralizing antibody titers: ACAM2000 + placebo groups: between 57 and 424 ACAM2000 + tecovirimat groups: between 20 to 107. All unvaccinated group and 2 tecovirimat-treated animals showed no detectable neutralizing antibody response.	Control group: A steep increase in viremia ($2x10^8$ genome copies/mL). Vaccinated group: Peak viral loads ≥1000-fold lower than control group.	The vaccinated group exhibited a lower number of lesions. The non-vaccinated control group succumbed on the 11th day after virus injection. One out of 25 vaccinated subjects died after infection.
(Iizuka et al., 2017)	In vivo	LC16m8 dan Lister (strain parental LC16m8) → 1 × 108 PFU/mL	*Cynomolgus monkeys* (*Macaca fascicularis*) Female (n=1); male (n=13) divided into 5 groups: Naïve (n=4), LC16m8-6M (n=3), LC16m8-12M (n=3), Lister-6M (n=2), and Lister-12M	MPXV Zr-599 (10^6 PFU)	Naïve group: Maximum IgG was shown at day 10. LC16m8- and Lister-vaccinated groups: IgG was induced immediately within 7 days.	LC16m8 or Lister group showed a reduction in viremia, meanwhile showed a very high plaque number.	Nearly no symptoms related to MPXV, whereas the majority of non-vaccinated subjects succumbed.

Author (Year)	Study Design	Methods			Outcome		
		Vaccine	Subject	Viruses	Antibody Titer	Viruses Level	Clinical Manifestation
			(n=2)				
(Hatch et al., 2013)	In vivo	ACAM2000 ((2,5 x10^5 to 12,5 x10^5 PFU)) Imvamune, modified vaccine virus Ankara-BN (MVA-BN) ((10^8 TCID50 in 0,5 ml total volume))	*Cynomolgus monkeys* (*Macaca fascicularis*) Female (n=12); male (n=12), divided into: control (*n* = 6), female Acam2000 group (*n* = 6), male Imvamune ×1 group (*n* = 6), and the female Imvamune ×2 group (*n* = 6)	MPXV Zaire 79, NR-2324. mean presented dose was 2.6 × 10^5 PFU	There is no significant difference (P > 0.05) in the level of neutralizing antibodies between a single dose of ACAM2000 (132 U/ml) group and those given a prime-boost Imvamune (69 U/ml).	After infection, live virus excretion was observed from the throat in 2 out of 6 animals in the prime-boost Imvamune group but not in the ACAM2000 group.	Side effects (vaccination site): Day 4: Red patches on Acam2000. Day 6: Raised scabbed sites (∼10 mm). Week 3: Dry scabs persisted. Imvamune group showed no reactive signs. After infection: Control group exhibited most severe weight decline (10-18%) From day 14: Acam2000, Imvamune ×1, and Imvamune ×2 group showed an increase in body weight indicating recovery phase.
(Townsend et al., 2013)	In vivo	Dryvax or ACAM2000 (2 × 10^5 PFU)	Prairie dog Dryvax (*n*=8), Acam2000 (*n*=9), Imvamune (*n*=10), and phosphate-buffered saline (PBS) (*n*=1) Human sera (vaccinees: aged 23 to 34 and 25 to 30) involving laboratory workers that is approved and monitored by the CDC Institutional Review Board (IRB) .	Basin MPXV-ROC-2003-385 (10^5 PFU)	From animals vaccinated with Dryvax and Acam2000, 70% exhibited a response to the WR148, H3, and D8 proteins, while 45% showed a response to each protein along with A13. Human responses to core proteins I1L, A10, and A4 were observed in Dryvax and Acam2000 vaccinees	Vaccinated human and prairie dog: No antigen was reactive	N/A
(Golden et al., 2012)	In vivo	Modified-vaccinia virus Ankara (MVA) , vaccine 4pox/L, ACAM2000 ($1×10^8$ pfu each vaccine group)	*Rhesus macaques* (*Maccaca mulatta*) Mice	MPXV strain Zaire-79 (2x 10^7 p.f.u)	4pox/LT and MVA groups showed dramatically reduced viremia level compared to control group. None of 4pox/LT group had titers $>10^4$.	MVA group showed viral shedding [500 pfu/ml to 6,725 pfu/ml (day 6)]. No virus shedding was found in 4pox/LT and ACAM2000 group.	The control group exhibited severe symptoms, whereas the groups vaccinated with ACAM2000 and MVA showed mild symptoms (few lesions).
(Gordon et al., 2011)	In vivo	Dryvax and LC16m8 (2.5 x	*Cynomolgus macaques* (n=24), divided into: Dryvax (n=4)	MPXV strain Zaire 79 (5x10^7	Both vaccinated groups showed neutralizing antibodies (2½	A significant lower levels of virus replication was shown by	The Dryvax and LC16m8 vaccines provided protection in the form of low

Author (Year)	Study Design	Methods			Outcome		
		Vaccine	Subject	Viruses	Antibody Titer	Viruses Level	Clinical Manifestation
		10^5 pfu each)	LC14m8 (n=14) Control (n=6)	pfu)	weeks post-exposure).	LC16m8 and Dryvax compared to control group ($P<$ .0001 and $P=$ .0095, respectively). Dryvax group exhibited lower viral loads (day 3 and day 6) compared with LC16m8 groups [not statistically significant ($P=$ .37 and $P=$ .076)]. No viral DNA was found on day 9.	virus levels and mild symptoms (symptoms resolving within 12-15 days after infection) in subjects with compromised immunity, characterized by low T and B cell counts, compared to the non-vaccinated group.
(Hirao et al., 2011)	In vivo	*Attenuated NYCBH vaccinia virus deleted for the E3L gene*	*Cynomolgus monkeys* (*Macaca fascicularis*) (n=24)	MPXV strain Zaire (5x10^7 PFU)	NYCBH group (1 dose) had significantly higher titers than mock-vaccinated group at day 42 (120, $p < 0.05$). NYCBHΔE3L group (2 doses) had 2-fold lower neutralizing antibody titers than NYCBH group (no statistically significant).	The NYCBHE3L-vaccinated group exhibited a significant number virus levels in the blood similar to the non-vaccinated group. However, the vaccinated group experienced a reduction in blood virus levels after infection.	The NYCBHE3L group survived death due to infection, but exhibited secondary skin lesions significantly. The vaccinated group showed a decrease skin lesions number, and an improvement in clinical scores 3 weeks after infection, compared to control group.
(Hirao et al., 2011)	In vivo	Multivalent Smallpox DNA Vaccine [125 µg of each plasmid (0.1 mL for ID and 0.5 mL for IM route in total volume)] Dryvax	*Cynomolgus macaques* (n=14) [controls (n=4), IM immunized (n=4), ID immunized (n=6)].	The Zaire strain, V79-I-005 (MPXV Master Seed NR-523) 2 x 10^7	ID group showed highest neutralizing antibodies induction (267 ± 159) compared to IM group (39±28). In an other experiment, the average titer of ID group (330 ± 126) was comparable to Dryvax group (407 ± 263).	Viremia level reduced significantly at day 12 in ID group by >3 logs (P=.01, Kruskal-Wallis) with <5,000 copies/mL (undetectable levels).	The vaccinated group exhibited a very small number of lesions compared to the control group (ID: 133±37; IM: 175±26). Only 1 animal from the control group survived MPXV infection but still showed severe symptoms in the form of numerous lesions on the last day of observation (day 27).
(Buchman et al., 2010)	In vivo	Modified vaccinia virus Ankara (MVA) (1x10^8 50% in Immavune, MVA-BN); Dryvax (2,5x10^5	Mencit SCID, DBA, A/Ncr, C3HeJ, IFN-ɣR-/-, and BALB/c	MPXV-ZAI-79 (5 µg/nare; 4.7 to 4,700 PFU intranasally)	Vaccinated group had higher antibody levels compared to the control group (0.34±0.04 and 0.07±0.02, P < 0.0006 at a 1:200 dilution).	N/A	Control group succumbed to the disease at day 11. Subject that received booster on −28 days pre-infection showed little weight loss compared to subjects that vaccinated once (significant weight

Author (Year)	Study Design	Methods			Outcome		
		Vaccine	Subject	Viruses	Antibody Titer	Viruses Level	Clinical Manifestation
		PFU)					loss on days 6, 7, and 8 p.i (P = 0.0002, 0.0002, and 0.0004, compared to control group). No significant microscopic lesions were found in internal organs.
(Keasey et al., 2010)	In vivo	Dryvax vaccine; ABLA/CpG/alum	*Cynomolgus monkeys* (*Macaca fascicularis*) 3-doses (16 females, 14 males); 2 doses (7 females; 5 males)	MPXV (NR523) (2×10^7 pfu)	Higher virus levels were found in the control group compared to the Dryvax group on days 3–15 ($P < 0.05$); in the ABLA(100)/CpG/alum group on days 3, 6, and 15 ($P < 0.05$); and in the ABLA(20)/CpG/alum group on days 3 and 15 ($P < 0.05$).	Control group: Peak viral loads were achieved by day 9 or 12 (10^7 - 10^9 genome copies/mL). Dryvax: No virus level was noted except for animal #4353 (~2×10^4 genome copies/mL on day 3). ABLA/CpG/alum: A significant lower virus level was found than control at day 3, 5, and 12.	Control group (unvaccinated): Typical signs of MPXV infection, lethargy, and depression were found, also, countless lesion were also observed by day 6. Dryvax: No death was found. All subjects showed a little or no clinical manifestation (few lesions were healed quickly). ABLA/CpG/alum: Subjects were protected from death.
(Zielinski et al., 2010)	In vivo	Smallpox vaccine (Dryvax, Wyeth)	*Cynomolgus macaques* (n=4) Human (n=4) who has received smallpox vaccine (Dryvax,Wyeth)	MPXV Zaire-1979_005 (5–100x10^4 pfu)	There is a significant increase in antibody response, specifically in IgM binding ($p \leq 0.01$), on the 6th day after subjects experienced infection compared to before infection.	N/A	N/A
(Zielinski et al., 2010)	In vivo	Smallpox vaccine with integrated IL-15 (Wyeth vaccinia derived from the Dryvax vaccine) 1×10^8 pfu	BALB/c and athymic congenic nude mice (CAnN.Cg-Foxn1nu/Crl); Cynomolgus macaques (Macaca fascicularis) (n=20)	MPXV (Zaire 79 MA-104 11/26/03) $5x10^7$ pfu	MVA/MVA derivatives showed 4-fold higher vaccinia plaque reduction neutralizing antibody titers (PRNT 80%) with integrated cytokines compared to Wyeth/Wyeth derivatives with integrated cytokines on week 6.	Day 3: Detectable viral loads were found in 25% of the subjects (1.4×10^4 to 1.8×10^6 genome copies/mL). Day 6: 4 subjects [CY19249 (Wyeth/IL-15), CY19251 (Wyeth/IL-15), CY1990 (Wyeth), CY128497 (MVA)] showed virus titers under the	All unvaccinated subjects succumbed to the disease. Fewer MPXV lesions were found and resolved sooner in 4 subjects [#CY128175 (Wyeth vaccinated), #CY66406 (MVA/IL-15 vaccinated), #CY19251 (Wyeth/IL-15 vaccinated), #CY19249 (Wyeth/IL-15 vaccinated)] than control group.

Author (Year)	Study Design	Methods			Outcome		
		Vaccine	Subject	Viruses	Antibody Titer	Viruses Level	Clinical Manifestation
						detection threshold. No detectable viral loads were observed in 3 of 4 subjects (CY19251, CY1990, and CY128497) during the entire study even though 3 years earlier they received vaccination.	
(Hooper et al., 2009)	In vivo	Dryvax vaccine ($2x10^5$)	*Cynomolgus monkeys* (18 females)	MPXV Zaire 79 5.0 x10^7 PFU IV	Vγ2Vδ2 T cells expanded for 3 weeks post-vaccination and a simple re-expansion was found in association with sterile anti-monkeypox virus immunity after MPXV exposure.	Vaccination provides complete protection against MPXV infection, with no detectable virus mRNA on days 4 through 27 following the initiation of infection.	Vaccinated group was fully protected without any lungs and other tissues lesions at week 4 p.i..
(Hooper et al., 2009)	In vivo	Virus-like replicon particles (VRP) expressing the vaccinia virus A33R, B5R, A27L, and L1R gene [4 VACV genes (10^8 VRP each) in the 4pox vaccine with total of 4×10^8 IU) Dryvax vaccine	*Cynomolgus macaques* (18 females)	*MPXV Zaire 79* 5 × 10^6 PFU	Virus-like particles (VRP) expressing the vaccinia virus genes A33R, B5R, A27L, and L1R provide protective immunity in mice comparable to vaccination with live vaccinia virus.	Virus genome level in vaccinated group was below the detection limit (<5000 genome copies/ml). Peak viral genome loads were shown in control group (5 to >6 logs) between day 9 and 12.	All subjects in the vaccinated group can survive without exhibiting severe symptoms, while the control group shows severe symptoms leading to death.
(Wei et al., 2009)	In vivo	Dryvax vaccine ($2x10^5$)	*Cynomolgus monkeys* (18 females)	MPXV Zaire 79 5.0 $x10^7$ PFU	Cidofovir+Dryvax group showed lower numbers of H3L-specific IFN-γ^+ cells compared to Dryvax-alone group significantly Cidofovir+Dryvax and Dryvax-alone group also exhibited higher recall immune responses of	Day 11: The cidofovir+Dryvax group showed lower mean viral copies of A33R than the mock control group significantly ($P < 0.05$) Day 28: No virus was found in	Control group: Severe clinical syndromes [respiratory disress, extremely low temperature (<94°F), disseminated intravascular coagulation, shock, or anorexia (>3 days) that led to moribundity on days 9, 11, or 14].

Author (Year)	Study Design	Methods			Outcome		
		Vaccine	Subject	Viruses	Antibody Titer	Viruses Level	Clinical Manifestation
					H3L-specific IFN-γ^+ T cells than the slow responses for the control group.	Dryvax-alone group. Cidofovir+Dryvax group geometrical mean levels (2 to 3 log) of live MPXV in fresh lung, skin, and lymph node tissues was lower than the control group.	Dryvax-alone group: At vaccination site, skin rash (red bumps on day 3 post-vaccination, later filled with pus and reaching a maximum size of 120 mm^2 on day 10 post-vaccination) was found. No death and notable clinical signs were found on day 28. Dryvax+cidofovir group: Minimal or no skin rash, with an average size of <20 mm2 ($p < 0.01$).
(Marriott et al., 2008)	In vivo	ACAM2000 4.4 × 10^8 pfu/mL Dryvax 1.5 × 10^8 pfu/mL	*Cynomolgus monkeys (n=24) Female (n=12); male (n=12)*	MPXV Zaire 3.8 × 10^7 IV	The neutralizing antibody titers generated by ACAM2000 are also equivalent to those produced by Dryvax.	The ACAM2000 vaccine showed a reduced virus replication.	The ACAM2000 vaccine has been proven to provide protection by the absence of significant clinical manifestations.
(Earl et al., 2008)	In vivo	MVA 1x10^8 infectious units Dryvax 2.5x10^5 infectious units	Cynomolgous monkeys (Macaca fascicularis) (n=50)	MPXV strain Zaire 79 5x10^7	≥6 days after MVA or Dryvax vaccination, subjects are clinically protected (except for 1 out of 16 vaccinated with MVA).	The viral load was generally higher in the MVA-vaccinated group.	The number of skin lesions are generally higher in the MVA group compared to Dryvax group.
(Karem et al., 2007)	Case control	*Smallpox vaccine-derived*	Human (n=72) (divided into: unvaccinated contacts, vaccinated contacts, unvaccinated cases, and vaccinated cases).	N/A	All cases groups were IgM, IgG, CD4, CD8, and B-cell positive (orthopoxvirus-specific), regardless of vaccination status.	N/A	Elevated levels of anti-orthopox virus IgG and smallpox vaccination in childhood were associated with the development of mild symptoms, although not significantly.
(Nigam et al., 2007)	In vivo	DNA/MVA HIV-1/AIDS vaccine (1x 10^8 PFU) Dryvax (1x10^8 PFU)	*Indian rhesus macaques* [DMM HIV (n=6); Dryvax (n=10)]	MPXV strain Zaire (5x10^7 PFU)	DMM HIV group exhibited similar vaccinia virus (VV)-specific antibody and 5–10-fold lower levels of VV-specific cellular responses compared to Dryvax group.	Subjects vaccinated with DNA/MVA HIV-1/AIDS exhibited low viremia levels between days 5 and 13. The Dryvax group showed undetectable viremia levels.	All vaccinated groups survived, while unvaccinated groups succumbed to the disease. Subjects vaccinated with DNA/MVA HIV-1/AIDS developed lesions between day 5 and 13, but returned to a healthy state by day 16.
(Earl et al., 2007)	In vivo	Recombinant Modified Vaccinia	*Rhesus macaques* [ID (n=9); IM (n=8); control (n=7)	MPXV (5x10^7)	VACV MV binding antibody levels had decreased to	The peak viral load in vaccinated group was	Non-vaccinated subjects exhibited severe symptoms, while immunized

Author (Year)	Study Design	Methods			Outcome		
		Vaccine	Subject	Viruses	Antibody Titer	Viruses Level	Clinical Manifestation
		Virus Ankara (MVA) ($1x10^8$ PFU)			<1:6400 and neutralizing titers to <1:563.	lower by 2.5 logs than the naïve group significantly ($p<0.0054$) from day 3 to 12.	subjects showed either minimal lesions that healed quickly or no lesions at all.
(Heraud et al., 2006)	In vivo	Recombinant subunit vaccines (smallpox vaccine Dryvax, a live vaccinia virus (VACV), L1R, A27L, A33R, and B5R) (4 plasmids (4 mg each): 3 mg i.m. and 1 mg intradermally.	*Rhesus macaques* (*Macaca mulatta*) (n=14)	MPXV Zaire 79 Strain ($5x10^7$)	Subjects who only received DNA failed to produce high antibody titers, similarly to the placebo control group.	MPXV genomes were detected mainly in DNA-only vaccinated group, consistent with the clinical manifestation.	Subjects who only received DNA experienced numerous uncountable skin lesions, and succumbed similarly to the placebo control group. Subjects vaccinated with protein exhibited moderate to severe symptoms (20–155 skin lesions) but survived. Subjects immunized with DNA followed by protein showed mild symptoms (<= 15 lesions) that resolved within days.
(Stittelaar et al., 2006)	In vivo	Modified Vaccinia Virus Ankara Elstree-RIVM ($2.5x10^5$ TCID50)	*Cynomolgus monkeys (Macaca fascicularis)* (n=34): untreated control (n=6), a human dose of Elstree-RIVM intracutaneously (n=6), 5 mg/kg cidofovir i.p. (n=12), 5 mg/kg HPMPO-DAPy i.p. (n=10).	MPXV strain MSF#6 10^7 PFU)	All surviving subjects showed MPXV-specific plasma IgG antibodies and MPXV-specific T cells (peripheral blood mononuclear cells) after the antiviral was terminated.	Cidofovir group showed lower viral load compared to control and vaccinated group significantly after 24 hours.	Control group: All subjects died on day 15 [mean: 12.6 days (range 9–19)]. Numerous cutaneous lesions, low O2 saturation, dyspnea, severe signs and symptoms were found. Elstree-RIVM group: One subject was protected from dead and severe morbidity. Cidofovir group: Survival and mild morbidity were observed in 5-dose regimen group (n=5), and 6-dose regimen group (n=4). This group reduced MPXV lesions significantly compared to control and vaccinated group after 24 hours. HPMPO-DAPy group:

Author (Year)	Study Design	Methods			Outcome		
		Vaccine	Subject	Viruses	Antibody Titer	Viruses Level	Clinical Manifestation
							Survival and protection against severe morbidity were observed in this group [5-dose regimen (n=2); 6-dose regimen (n=5)].
(Saijo et al., 2006)	In vivo	*Highly Attenuated Vaccinia Virus Vaccine* (LC16m8) ($1x10^8$ PFU/mL)	*Cynomolgus monkeys (Macaca fascicularis)* (1 male; 14 female)	MPXV strains Liberia and Zr-599 ($1x10^6$ PFU)	Neutralizing antibody was shown in LC16m8 and Lister group and was not increased after MPXV exposure.	Viremia levels and durations were highest in SC-Naïve group, followed by SC-LC16m8 group. Intranasal group: Viremia was shown in IN-Naïve group. The IN-Lister or IN-LC16m8 groups didn't show any viremia. Subcutaneous group: Viremia was shown in all group, except 1 for 2 subjects in SC-Lister group.	Control group: Weight loss was observed at about 15%. Severe symptoms were shown on day 7. SC-Lister group: Body weight was maintained. MPXV-related symptoms weren't found. SC-LC16m8 group: Body weight was maintained. Any MPXV-related symptoms weren't detected.
(Stittelar et al., 2005)	In vivo	Classical vaccinia virus-based smallpox vaccine (Elstree-RIVM) ($2,5x\ 10^5$ $TCID_{50}$) MVA-BN ($2x10^8$ PFU) Dryvax ($2,5x\ 10^5$ $TCID_{50}$)	*Cynomolgus monkeys* (*Macaca fascicularis*) (n=35) Group I: MVA-BN (10^8 PFU) via s.c. on day -28 and 0 Group II: MVA-BN primer dose ($2x10^6$ PFU) via s.c. on day-10 and Elstree-RIVM via i.c. on day 0. Group III: Elstree-RIVM via i.c. on day 0 Group IV: Elstree-BN via i.c. on day 0 Group V: non-vaccinated subjects	MPXV strain MSF#6 (10^6 or 10^7 PFU)	Strongest neutralizing antibodies responses were recorded and declined gradually until challenge day in group 1. At this time, there was a significant differences between group I and IV ($P=0.004$), and group I and III ($P<0.001$), where the highest titers were shown by group III and the lowest titers were shown by group I.	Virus kinetics in vaccinated group reached its peak on day 6 and 8. Then, it gradually declined afterward until became aviremic significantly compared to control group.	Control animals: Elevated body temperature (>1°C; ~2.65%), anorexia, dyspnea, conjunctivitis, nasal discharge, pocks (50-100), and lethargic were shown. Vaccinated groups: Only 1 subject (MVA-BN) in vaccinated groups showed pocks (initially developed >70 lesions on day 11, then completely resolved on day 28, and less progressive than control group).
(Edghill-Smith et al., 2005)	In vivo	Dryvax	*Rhesus macaques (Macaca mulatta)* (n=32)	MPXV strain Zaire ($5x10^7$ PFU)	Neutralizing antibody titers (between 120 and 3,500) were shown in groups 1 and 3 to vaccinia, while group 2 did not	Viral genomes in blood were not detected in all subjects who had CD4+ depletion on day 3. No MPXV viral	All subjects who had CD8+ T cells depletion did not show any skin lesions.

Author (Year)	Study Design	Methods			Outcome		
		Vaccine	Subject	Viruses	Antibody Titer	Viruses Level	Clinical Manifestation
					had equivalent levels of titers to vaccinia. Humoral response against Dryvax was affected by the depletion of B-cells.	genomes were found in group 3, which showed that Dryvax could induce protection.	
(Hooper et al., 2004)	In vivo	4pox DNA vaccine L1R DNA vaccine Hantaan virus DNA vaccine Dryvax	*Rhesus macaques* Group 1 (n=3): 4pox DNA vaccine Group 2 (n=2): L1R DNA vaccine Group 3 (n=3): Negative controls vaccinated with a Hantaan virus DNA vaccine Group 4 (n=2): Positive controls vaccinated with Dryvax.	MPOV Zaire-79 (MPOV-Z79) (5 x10^8 PFU)	Dryvax group developed very different antigen-specific antibody responses. 4pox DNA vaccine subjects (n=2) were A27L, B5R, and A33R positive but not L1R. L1R DNA vaccine group showed relatively high L1R-specific antibody responses than 4pox DNA vaccine (CH93) group.	The most protected subject was 4pox DNA vaccine (CH93) monkey (n=1) other than Dryvax group, with no virus in oral secretion, no viremia, and one lesion. Oral secretions: Dryvax and 4pox DNA vaccine group did not show any viruses. On day 4, 4pox and L1R DNA vaccine groups showed infectious viruses. Interestingly,viruses were not shown in negative control group until 6 days later. Blood: 4pox DNA vaccine, L1R DNA vaccine, or Dryvax did not show any infectious viruses. Meanwhile, viruses were detected in the negative control group.	Control group: Severe signs and symptoms leading to death were found. Dryvax group: No clinical signs were shown. DNA-vaccinated group (L1R, A27L, A33R, and B5R): No severe clinical signs were shown.
(Hooper et al., 2003)	In vivo	Four-gene combination DNA vaccine (3.4 x 10^7 PFU)	*Rhesus macaques; mice*	MPXV strain zaire 79	Mice that received separate DNA vaccines containing two distinct VACV immunogens, A27L (IMV immunogen) or B5R (EEV immunogen), did not exhibit significant protection. Both	N/A	N/A

Author (Year)	Study Design	Methods				Outcome	
		Vaccine	Subject	Viruses	Antibody Titer	Viruses Level	Clinical Manifestation
					genes combination resulted in a substantial level of protection and MPXV orthologous proteins cross-reactivity.		

DISCUSSION

Our systematic review demonstrates that the smallpox vaccine, previously used against variola, can provide protection against MPXV. There are two types of smallpox vaccines used: live attenuated vaccines and subunit vaccines made from protein, virus-like replicon particles, and DNA virus. The overall results show that post-exposure vaccination protects subjects and can induce long-term protection against severe and fatal MPXV infection. The live attenuated smallpox vaccine is the most commonly used type of vaccine in various studies against MPXV infection, including Dryvax, ACAM2000, Imvamune, LC16m8, and Lister. ACAM2000 can reduce virus replication post-infection and does not show significant clinical signs of MPXV infection. The neutralizing antibody titers produced by ACAM2000 are equivalent to those produced in the currently approved vaccine, Dryvax (Marriott et al., 2008).

Animals vaccinated with a single dose of Imvamune are not fully protected from severe and/or fatal infection, while animals receiving both prime and booster doses of Imvamune or a single dose of Acam2000 achieve full protection (Hatch et al., 2013). Monkeys immunized with LC16m8 show no symptoms of monkeypox except for mild ulcers at the site of virus inoculation (Saijo et al., 2006). LC16m8 can reduce viremia and induce IgG antibody response. Vaccination of monkeys with a single dose of LC16m8 provides protection against MPXV for over a year after immunization, indicating that vaccination with LC16m8 in humans can induce long-term protection (Iizuka et al., 2017). A study suggests that LC16m8 vaccine is a safer and more effective alternative to ACAM2000 and Dryvax for individuals with immune disorders (Gordon et al., 2011). Additionally, monkeys immunized with Lister show no symptoms of monkeypox (Saijo et al., 2006). Subunit vaccines against MPXV can also be a safer alternative compared to live attenuated vaccines. DNA/MVA vaccines produce specific levels of vaccinia virus (VV)-specific antibodies similar to Dryvax and provide long-term protective immunity (up to 3 years) (Nigam et al., 2007). Subunit orthopoxvirus vaccines given on the same schedule can also provide protection levels at least as high as MVA (Golden et al., 2012).

A single-dose vaccination regimen consisting of Dryvax and the antiviral agent cidofovir can reduce vaccinia viral load and significantly control vaccination side effects. Additionally, the immune response elicited by the vaccine, including antibodies and T-effector cells, is also reduced. This suggests that this combination compromises the immunity induced by Dryvax against monkeypox, although vaccinated monkeys show protection against MPXV compared to controls (Wei et al., 2009). Clinical signs of disease were also reported to increase in animals treated with ACAM2000 and tecovirimat compared to animals given a placebo (Russo et al., 2020).

CONCLUSION

This systematic review found that the overall potential of smallpox vaccines is quite satisfactory in preventing MPXV infection. Post-exposure vaccination protects subjects and provides long-term protection against severe MPXV infection. Subunit vaccines against MPXV could also be a safer alternative compared to live attenuated vaccines. Smallpox vaccination is still recommended for

high-risk groups at risk of monkeypox infection. Specific vaccines for monkeypox infection are still being developed.

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