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SYSTEMATIC REVIEW

Maternal and Pediatric Use of Vaccines for Mpox: A Living Systematic Review and Meta-analysis of Safety and Effectiveness

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Abstract

Background Mpox is a re-emerging zoonotic infection caused by an *Orthopoxvirus* closely related to smallpox. The 2022–23 global outbreak prompted rapid use of vaccinia-based vaccines, historically developed for smallpox and those of the latest generation used for mpox prevention. Assessing their safety and effectiveness in pregnant persons and children is critical to guide policies protecting populations at an elevated risk of severe illness.

Objective This study assessed the safety and effectiveness of mpox and historical smallpox vaccines, administered during pregnancy and childhood.

Methods We conducted a living systematic review and meta-analysis (PROSPERO CRD42024591322/CRD42024586205) following Cochrane, World Health Organization, and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) standards. We searched biweekly across major databases, trial registries, preprints, and gray literature (inception to September 2025) for studies evaluating the safety and effectiveness of vaccinia-based smallpox vaccines, including historical (first- and second-generation) and modern (third-generation) vaccines, in maternal and pediatric populations. Reviewers independently conducted study selection, data extraction, and risk-of-bias assessment. Meta-analyses employed random-effects models, and results are presented through an interactive dashboard and a living platform.

Results We included 27 clinical studies (1949–2025), involving 1,406,771 children/adolescents (eight studies) and 11,482 pregnant persons (19 studies). Most maternal data came from first-generation vaccines (Lister, Finnish, Dryvax, APSV). These vaccines were not associated with an increased risk of spontaneous abortion (risk ratio [RR] 1.02, 95% confidence interval [CI] 0.70–1.48), stillbirth (RR 1.02, 95% CI 0.70–1.48), or preterm birth (RR 1.08, 95% CI 0.78–1.50), but were linked to a higher risk of congenital anomalies (RR 1.25, 95% CI 1.01–1.54). Fifty-two fetal vaccinia cases were reported globally up to 1978, with none since. Evidence on second- (ACAM2000) and third-generation (MVA-BN) non-replicating vaccines remains limited. In children, serious adverse events were rare, and MVA-BN caused only mild self-limiting reactions. No study assessed vaccine effectiveness in pregnant persons, while limited pediatric data suggested possible protection after post-exposure prophylaxis.

Conclusions Vaccinia-based vaccines appear generally safe in pregnancy and children. However, evidence on the safety and effectiveness of third-generation mpox vaccines is still scarce. High-quality prospective studies and strengthened pharmacovigilance are urgently needed to inform policy and clinical decision making.

1 Introduction

Mpox (formerly known as monkeypox) is a re-emerging zoonotic disease caused by the monkeypox virus, a member of the *Orthopoxvirus* genus closely related to variola virus, the causative agent of smallpox [1]. Mpox is transmitted primarily through close physical contact and respiratory droplets, with enhanced person-to-person transmission driving sustained outbreaks in non-endemic settings;

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Key Points

Vaccinia-based vaccines have generally shown a favorable safety profile in pregnant persons and children, although evidence varies by vaccine generation.

While first-generation vaccines were associated with a slightly increased risk of congenital anomalies, no increased risk of adverse pregnancy outcomes has been observed with second- and third-generation vaccines; in children, serious adverse events are rare and typically mild and self-limiting.

Safety data for third-generation mpox vaccines in pregnancy and pediatric populations remain limited, underscoring the need for high-quality studies and strengthened pharmacovigilance to guide vaccination policies in the context of ongoing outbreaks.

sexual networks have been identified as predominant transmission routes in multiple regions [2]. Young adults have comprised most reported cases in non-endemic outbreaks, but pregnant persons, children (notably those under 5 years of age), and immunocompromised individuals are at higher risk of severe disease and complications [3]. Historically limited to Central and West Africa, the 2022–23 Clade IIb mpox global outbreak led to unprecedented international spread, prompting the World Health Organization (WHO) to declare a Public Health Emergency of International Concern and the Africa Centres for Disease Control and Prevention to declare its first-ever public health emergency [4, 5]. Mpox has been confirmed in over 115 countries across all six WHO regions, with tens of thousands of laboratory-confirmed cases reported globally, underscoring its rapid spread beyond previously affected regions [6]. Since 2024, a second outbreak associated with Clade I mpox continues to affect primarily children and families, highlighting the virus' adaptation for human-to-human transmission [6]. Early guidance from the WHO on mpox clinical management and immunization strategies has emphasized targeted use of available vaccines and adaptive public health responses, highlighting the need for ongoing evidence synthesis as outbreak dynamics and vaccination policies evolve [7]. Health authorities mobilized existing smallpox vaccines, primarily third-generation non- or minimally replicating formulations, for prevention and outbreak control. These vaccines, such as MVA-BN (Modified Vaccinia Ankara-Bavarian Nordic, manufactured by Bavarian Nordic A/S, Denmark) and LC16m8 (manufactured by the Chemo-Sero-Therapeutic Research Institute [Kaketsuken], Japan), were initially developed for smallpox prevention and are used for mpox based on evidence of immunological cross-protection [8].

Despite their widespread use, pregnant persons, neonates, infants, and children were largely excluded from vaccine trials and observational studies [9]. This fact is concerning, given the substantial risk of adverse outcomes after infection in these groups. Among pregnant persons, high rates of fetal loss, vertical transmission, and severe perinatal outcomes have been described in meta-analyses and outbreak data from Africa [10–14]. A systematic review included 11 pregnancies, and 63% had adverse outcomes, with vertical transmission in 79% of them [11]. Another study, including 33 pregnancies, reported miscarriage and stillbirth rates of 9.1% and 6.1%, respectively [15]. In endemic settings, Clade I infections have been associated with a perinatal mortality rate of nearly 75%. By contrast, the 2022–23 Clade IIb outbreak showed fewer adverse perinatal outcomes, suggesting possible differences in virulence [16].

Physiological and immunological changes during pregnancy and early life can alter vaccine responses and benefit-risk profiles, underscoring the need for dedicated and ongoing evaluation of these factors [17–20]. Yet, no mpox vaccine trial has enrolled pregnant persons or children. Ongoing studies are recruiting infants and children to assess the safety and immunogenicity of MVA-BN [21–24]. However, pivotal studies informing the regulatory approval of smallpox vaccines for use in the mpox outbreak, primarily MVA-BN and LC16m8, were conducted in healthy adult populations, often before the mpox outbreak, and were initially designed for smallpox preparedness [25–28]. Observational data from the 2022–23 global outbreak reported minimal maternal or pediatric data [18, 29, 30]. Given the rapidly evolving global epidemiology and the relative paucity of high-quality comparative trials in key subpopulations, a living systematic review (LSR) is warranted to continuously integrate emerging evidence, particularly from real-world observational safety and effectiveness data of vaccinia-based vaccines, administered during pregnancy and childhood [31, 32]. This LSR will guide vaccine policy in dynamic public health contexts through dashboard and living meta-analyses hosted on the Safe in Pregnancy/Safe in Children public platform (www.safeinpregnancy.org/), providing open public access to updated evidence for researchers and policy makers.

Table 1 Characteristics of historical smallpox vaccines (first and second generation) and vaccines used for mpox prevention (third- and fourth-generation) vaccines

Vaccine product	Composition (strain)	Generation	Phase of development	Status	Year of approval for mpox	Country of approval	Target population
Lister	Live VACV (Lister)	First-generation replicating VACV	Not applicable	Discontinued	Not applicable	Not applicable	Not applicable
Finnish	Live VACV (Finnish)	First-generation replicating VACV	Not applicable	Discontinued	Not applicable	Not applicable	Not applicable
Dryvax	Live VACV (NYCBH)	First-generation replicating VACV	Not applicable	Discontinued	Not applicable	Not applicable	Not applicable
APSV	Live VACV (NYCBH)	First-generation replicating VACV	Not applicable	Discontinued	Not applicable	Not applicable	Not applicable
ACAM2000	Live VACV (NYCBH)	Second-generation replicating VACV	IV	Approved	2024	USA	Subjects at high risk
MVA-BN	Live modified VACV (Ankara)	Third-generation non-replicating VACV	IV	Approved	2019	USA/EMA	Age ≥ 18 years at high risk
LC16m8 KMB	Live modified VACV (Lister)	Third-generation replicating VACV	IV	Approved	2024	Japan/WHO	≥ 1 year
VACΔ6/OrthopoxVac	Live genetically modified VACV (Lister)	Fourth-generation non-replicating VACV	II/III	Approved	2022	Russia	18–60 years
NYVAC	Live genetically modified VACV (Copenhagen)	Fourth-generation non-replicating VACV	I/II	In development	In development	In development	In development
mRNA-1769	mRNA	Not applicable	I/II	In development	In development	In development	18–49 years
BNT166a	RNA	Not applicable	I/II	In development	In development	In development	18–65 years

EMA European Medicines Agency, *Live* live attenuated virus, *VACV* vaccinia virus, *WHO* World Health Organization

2 Methods

We conducted this LSR in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [33], WHO tools [34], Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [35], and PRISMA-LSR reporting standards [36], and we registered it in PROSPERO (CRD42024586205 [37] and CRD42024591322 [37]).

2.1 Inclusion Criteria

We planned to include randomized controlled trials, quasi-experimental studies, cohort studies, case-control studies, cross-sectional studies, case series, and case reports (only for novel adverse events) assessing the safety (any outcome) and efficacy/effectiveness (infections, hospitalizations, and disease-related death) of any vaccinia-based vaccines administered to children, adolescents, and pregnant persons. The following age-group categories were defined a priori and applied throughout the article and corresponding dashboard visualizations. Neonates were defined as infants from birth to 28 days of life, children as individuals aged older than 28 days and younger than 12 years, and adolescents as individuals aged 12–17 years. The term pediatric was used as an umbrella category encompassing neonates, children, and adolescents (aged < 18 years). The results for the adult population will be reported in a separate publication. Interventions of interest included mpox and historical smallpox vaccines, regardless of their generation (Table 1). Comparators encompass active or inactive interventions that are not under evaluation, standard care, or a placebo. Non-comparative study designs were eligible.

2.2 Search Strategy and Selection of Studies

We conducted comprehensive biweekly searches without language or date restrictions from database inception to September 2025 across MEDLINE [38], EMBASE [39], CENTRAL [40], LILACS [41], and the Cochrane Library [42], in addition to clinical trial registries (e.g., ClinicalTrials.gov [43], WHO International Clinical Trials Registry Platform [44]), preprint servers (e.g., medRxiv [45], bioRxiv [46]), professional society guidelines, mpox-specific research hubs, regulatory agencies (e.g., US Food and Drug Administration [47], European Medicines Agency [48]), relevant conference abstracts, reference list, and contact with experts. The entire search strategy is available in the PROSPERO registry and in Table S1 of the Electronic Supplementary Material (ESM) [37]. Pairs of reviewers independently screened titles and abstracts and the full texts of eligible records using the Nested Knowledge platform [49].

2.3 Data Collection and Risk of Bias Assessment

Pairs of reviewers extracted data independently using REDCap [50] forms, which were piloted on a sample of ten studies. We contacted the authors of the studies when needed to clarify missing or unclear data. Each pair assessed the risk of bias using the ROBINS-I [48] tool for comparative observational studies, including cohort and case-control designs, and the National Institutes of Health Quality Assessment Tool [51] for non-comparative study designs, including case series and case reports. We did not apply other tools described in the protocol, as we lacked study designs such as randomized controlled trials [52], time series, and before-and-after studies [37]. Results were summarized using the GRADE approach to assess the certainty of evidence [53]. Given the living nature of the LSR, GRADE assessments are updated iteratively as new evidence becomes available. We did not assess the risk of bias for preclinical studies. Discrepancies were resolved by consensus.

2.4 Data Synthesis and Data Visualization

The LSR entails a comprehensive and ongoing search for all relevant studies on mpox vaccines, encompassing both preclinical and clinical data. In this article, we conducted a focused analysis of clinical studies specifically involving pregnant persons and children to inform recommendations for mpox vaccination in these at-risk populations directly.

We performed random-effects meta-analyses for comparative studies and proportion meta-analyses for non-comparative studies, using the R packages Meta, Metafor, and tidyverse [54]. Outcome measures included odds ratios, risk ratios (RRs), hazard ratios, vaccine effectiveness (VE), and mean differences with 95% confidence intervals (CIs). We performed stratified analyses by population and pre-specified subgroup analyses by vaccine generation, product or platform, age interval, geographic region, mpox clade (when available), and a sensitivity analysis by excluding poor-quality/high-risk-of-bias studies to assess the robustness of pooled estimates. For studies with zero events in one or both arms, we applied a treatment-arm continuity correction, in which the continuity correction is weighted according to the sample size of each study arm, rather than using a fixed 0.5 correction [55]. Proportion meta-analyses were used to descriptively to summarize event frequencies and do not imply comparative safety or causality. Historical background rates for neonatal outcomes were provided where available for contextual interpretation only rates provide essential reference points for contextualizing our findings [56], and comparative inference was restricted to studies with explicit comparator groups. Analyses were planned a priori and conducted separately for pre- and post-exposure vaccination contexts, recognizing their distinct objectives, and implications for effectiveness and safety assessments.

We present updated data through a public and dynamic platform that includes a Microsoft Power BI [57] dashboard and a living meta-analysis tool developed in Shiny (RStudio) [58]. These tools allow users to filter and explore results by age, region, vaccine platform, and other relevant variables stratified by population. This approach enhances transparency and facilitates the rapid uptake of evidence. Systematic searches are conducted every 15 days, and dashboards are automatically updated as new eligible studies are incorporated. Each update is dated to ensure transparency over time. Repeated meta-analyses are recalculated dynamically, with an explicit display of statistical uncertainty, study-level risk of bias, and GRADE certainty ratings to support correct interpretation of evolving evidence.

3 Results

For the entire LSR, we screened 4169 records and included 146 studies in the review (Fig. 1, study flow diagram). Of these, 31 were preclinical and 114 were clinical, encompassing 3,162,705 individuals who had been vaccinated. We included here 27 clinical studies involving 1,406,771 children and adolescents (eight studies) and 11,482 pregnant persons (19 studies). Cohort studies were the most frequent design (n = 22), followed by case-control studies, case series, cross-sectional studies, and case reports (one each) (Table 2). We also provide a list of the clinical studies initially included and ultimately excluded, along with the reasons for exclusion (Table S2 of the ESM).

Nineteen studies published between 1949 and 2025 reported vaccination during pregnancy with either first-generation replicating vaccinia virus (VACV) vaccines

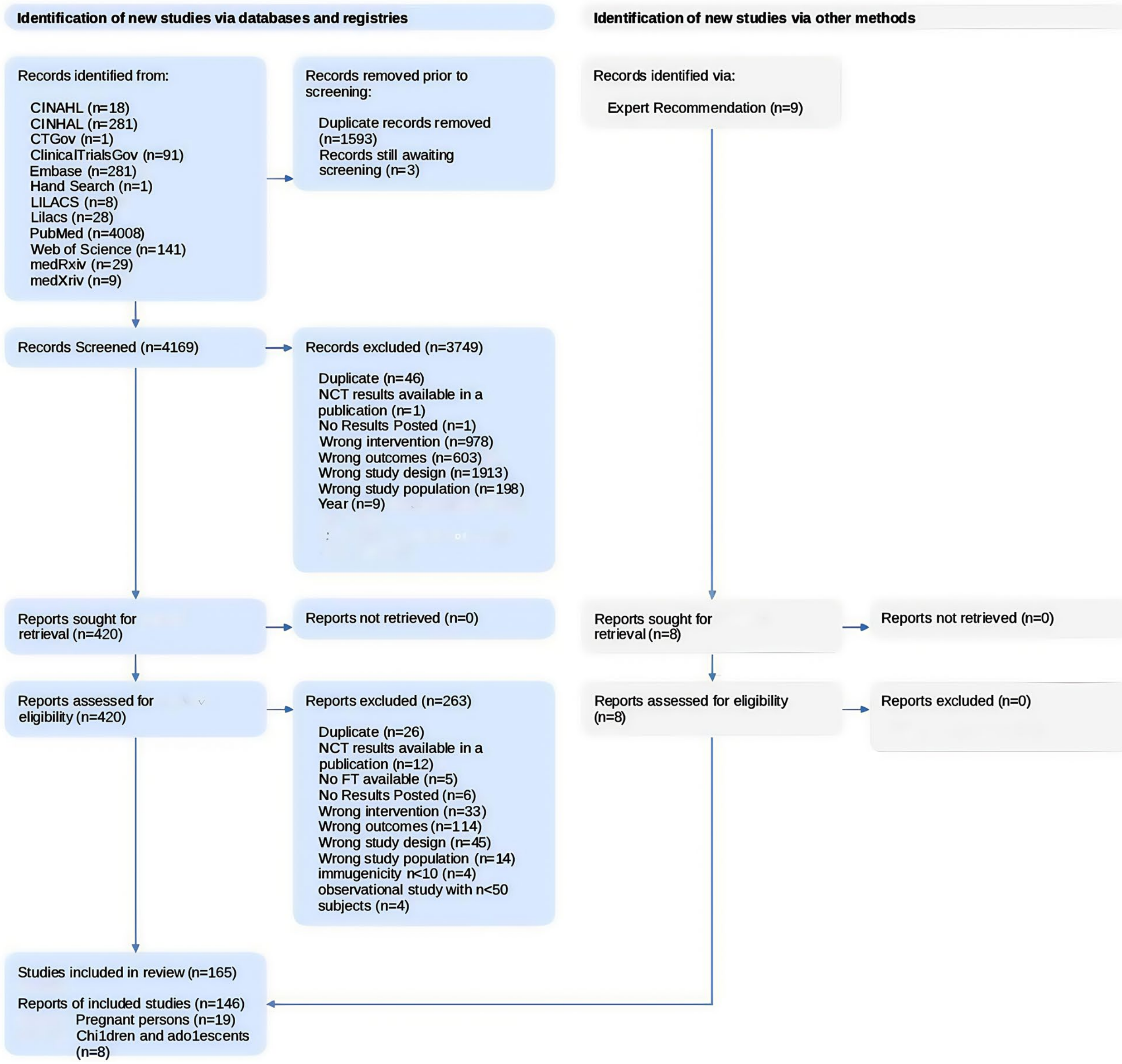

Fig. 1 Study flow diagram

(Dryvax, Lister, Finnish strains, unspecified strain; n = 16) or a third-generation, non-replicating *vaccinia*-based vaccine (MVA-BN, n = 2). All vaccinations occurred as pre-exposure prophylaxis, mainly during the 20th-century smallpox eradication campaign or, more recently, for smallpox occupational protection (e.g., military personnel). The study populations were predominantly from the USA (n = 6), followed by the UK (n = 2) and Poland (n = 2), multi-country (n = 2), with single studies from the Democratic Republic of Congo, Finland, Iran, Ireland, Russia, South Africa, and Sweden (Table 2).

Eight studies, including those involving children and adolescents (aged <18 years), published between 1970 and 2024, assessed four distinct vaccine products: MVA-BN (4), Dryvax (2), ACAM2000 (1), and LC16m8 (1). They were conducted in the USA (n = 5), Canada, Japan, and the UK (one each). The approaches of this intervention included pre-exposure prophylaxis (n = 6) used for smallpox and mpox outbreaks, post-exposure prophylaxis, and both (one each using MVA-BN for mpox outbreak) (Table 2).

Our interactive platform, https://www.safeinpregnancy.org/living-systematic-review-mpox/, presents results by population, region, vaccine product/generation, immunization strategy, and study design (Fig. 2). The platform enables the conduction of pairwise and proportional living

Table 2 Characteristics of clinical studies

Vaccine platform	Vaccine	Author year	Country	Study design	Age range	Vaccinated (*N*)	Dosage	Number of doses	Outcomes
Pregnant persons									
LAV VACV	MVA-BN	Priyamvada 2022 [61]	Congo, Dem. Rep.	Cohort	18–59 years	14	0.5 mL	2	S, Im
		Suñer 2025 [64]	Spain, Peru, Panama, Chile	Case report[b]	29-year-old woman	1	0.1 mL intradermal	1	S
VACV	NR[$]	Lane 1971 [65]	Worldwide	Case series	NR	NR	NR	1	S
		CDC 1979 [66]	USA	Case series	NR	NR	NR	1	S
		Naderi 1975 [77]	Iran, Islamic Rep.	Cohort	NR	1522	NR	1	S
		Ladnyĭ 1974 [71]	Russian Federation	Cohort	NR	1172	NR	1	S
		Janiszewski 1966 [78]	Poland	Cohort	NR	205	NR	1	S
		Abramowitz 1957 [79]	South Africa	Cohort	NR	1121	NR	1	S
		Bieniarz 1956 [80]	Poland	Cohort	NR	495	NR	1	S
		Macarthur 1952 [81]	UK	Cohort	NR	170	NR	1	S
	Finnish strain	Saxen 1968 [82]	Finland	Case Control	18–35 years	107	10^8 PFU/1 mL	1	S
	Lister	Engström 1966 [83]	Sweden	Cohort	17–43 years	170	NR	1	S
		Bourke 1964 [84]	Ireland	Cohort	18–35 years	112	10^7–10^8 viral particles/mL	1	S
		Liebeschue 1964 [85]	UK	Cohort	NR	157	10^7–10^8 PV/mL	1	S
	Dryvax	Ryan 2008 [60]	USA	Cohort	17–41 years	376	NR	1	S
		Ryan 2008 [63]	USA	Cohort	< 18 to > 35 years	882	1.6×10^8 PFU/1 mL	1	S
		Wentworth 1966 [86]	USA	Cohort	NR	65	NR	1	S
		Bellows 1949 [87]	USA	Cohort	<18 to > 35 years	720	1.6×10^8 PFU/mL	1	S
		Greenberg 1949 [62]	USA	Cohort	NR	4172	1.6×10^8 PFU/mL	1	S
Children/adolescents									
LAV VACV	MVA-BN	Duffy 2024 [88]	USA	Cohort	0 to ≥ 65 years 0–18 years	0[a] NR	0.1/0.5 mL	1	S
		Muller 2024 [89]	Canada	Cohort[BothE]	12 to ≥ 80 years 12–18 years	1173 11	0.5 mL	1	S, Ef
		Ladhani 2023 [9]	UK	Cohort[PosE]	28 days to 18 years	87	0.5 mL	1	S, Im, Ef
		Sharff 2023 [90]	USA	Cohort	12–82 years 12–18 years	2126 NR	0.1/0.5 mL	2	S
	LC16m8	Yamaguchi 1975 [68]	Japan	Cohort	2–12 years	100,340	2.5×10^7 PFU/0.5 mL	1	S

Table 2 (continued)

Vaccine platform	Vaccine	Author year	Country	Study design	Age range	Vaccinated (*N*)	Dosage	Number of doses	Outcomes
VACV	ACAM2000	Decker 2021 [91]	USA	Cohort	12–0 years 12–18 years	131,274 NR	NR	1	S
	Dryvax	Lane 1970 [72]	USA	Cross-sectional	0–18 years	59	1.6 × 10^8 PFU/mL	1	S
		Lane 1970 [67]	USA	Cohort	28 days to 18 years	1,175,000	NR	2	S

BothE pre- and post-exposure prophylaxis, *Ef* effectiveness, *Im* immunogenicity, *LAV* live attenuated, *NR* not reported, *PosE* post-exposure prophylaxis, *S* safety, *VACV* vaccinia virus

[a]Data from the Vaccine Adverse Event Reporting System (2022–23) indicate a total of 1,207,056 vaccine doses administered—744,075 first doses and 462,981 second doses—including both children and adults. However, the exact number of children who received one or two doses could not be determined

[b]Case report of an unnoticed vaccination during 4 weeks of pregnancy in the context of a prospective target trial emulation for an adult population

meta-analyses, https://www.safeinpregnancy.org/comparative-and-proportional-meta-analyses-mpox.

3.1 Risk of Bias of Included Studies

Among the cohort and cross-sectional studies, 60% (6/10) have a poor-quality rating (high risk of bias), 30% (3/10) a fair rating, and 10% (1/10) a good rating (Table S3 of the ESM). The single case-control study presented a fair risk of bias (Table S4 of the ESM). In contrast, the systematic review by Badell et al., which contributed non-comparative case-series data streams, the underlying evidence as, was rated as having poor quality (Table S5 of the ESM). We could not assess the risk of bias of the five studies extracted from the systematic review by Badell et al. [59].

Regarding eight studies in children and adolescents, seven were cohort studies and one was cross-sectional; 38% (3/8) presented a poor-quality rating, 50% (4/8) a fair rating, and 12% (1/8) a good rating (Table S6 of the ESM). To evaluate the risk of bias in the single-cohort study with available data for assessment [56], we used the ROBINS-I-V2 tool. The study was classified as moderate risk of bias (Table S7 of the ESM).

3.2 Effects of mpox and Historical Smallpox Vaccines Administered During Pregnancy

3.2.1 Maternal Pregnancy-Related Outcomes

Data regarding maternal pregnancy-related outcomes were derived predominantly from first-generation replicating VACV administered during smallpox eradication campaigns. In the pairwise meta-analysis, these first-generation vaccines, compared with no vaccination, were not significantly associated with spontaneous abortion (pooled RR 1.02, 95% CI 0.70–1.48; $I^2 = 60\%$; eight studies, 4061 vaccinated pregnant persons). Similarly, the RR for stillbirth was 1.56 (95% CI 0.79–3.09; $I^2 = 0\%$; three studies, 974 vaccinated pregnant persons). The certainty of evidence and the absolute effects for these outcomes are summarized in Table 3. In the proportional meta-analysis (Table 4), across six studies reporting spontaneous abortion after first-generation vaccination, the pooled proportion was 4.45 per 100 pregnancies (95% CI 1.15–9.46; $I^2 = 86\%$; based on eight studies among 1342 vaccinated pregnant persons). For stillbirth, the pooled proportion was 2.95 per 100 vaccinated pregnant persons (95% CI 1.54–4.36; $I^2 = 65\%$; nine studies, 1943 vaccinated pregnant persons).

A sensitivity analysis, excluding studies of poor quality, generally supported the primary findings. In the National Smallpox Vaccine in Pregnancy Registry (Ryan et al. [60]), a study designed to capture inadvertent vaccination during pregnancy, the proportion of spontaneous abortion increased to 9.84% (95% CI 7.02–13.31), while the proportion of stillbirths rose modestly to 3.59% (95% CI 0.10–11.0). The other results were consistent with the primary analysis (see Table S7 of the ESM).

Evidence on third-generation non-replicating vaccines in pregnancy was extremely limited and based on small sample sizes. One study reported an estimated frequency of stillbirths of 7.14 per 100 vaccinated pregnant persons (95% CI 0.18–33.87; based on 14 vaccinated pregnant persons) [61]. No study provided detailed information on specific adverse events following immunization in pregnant persons, underscoring the paucity of evidence in this population and highlighting the need for further research on the safety profile of newer smallpox vaccines during pregnancy.

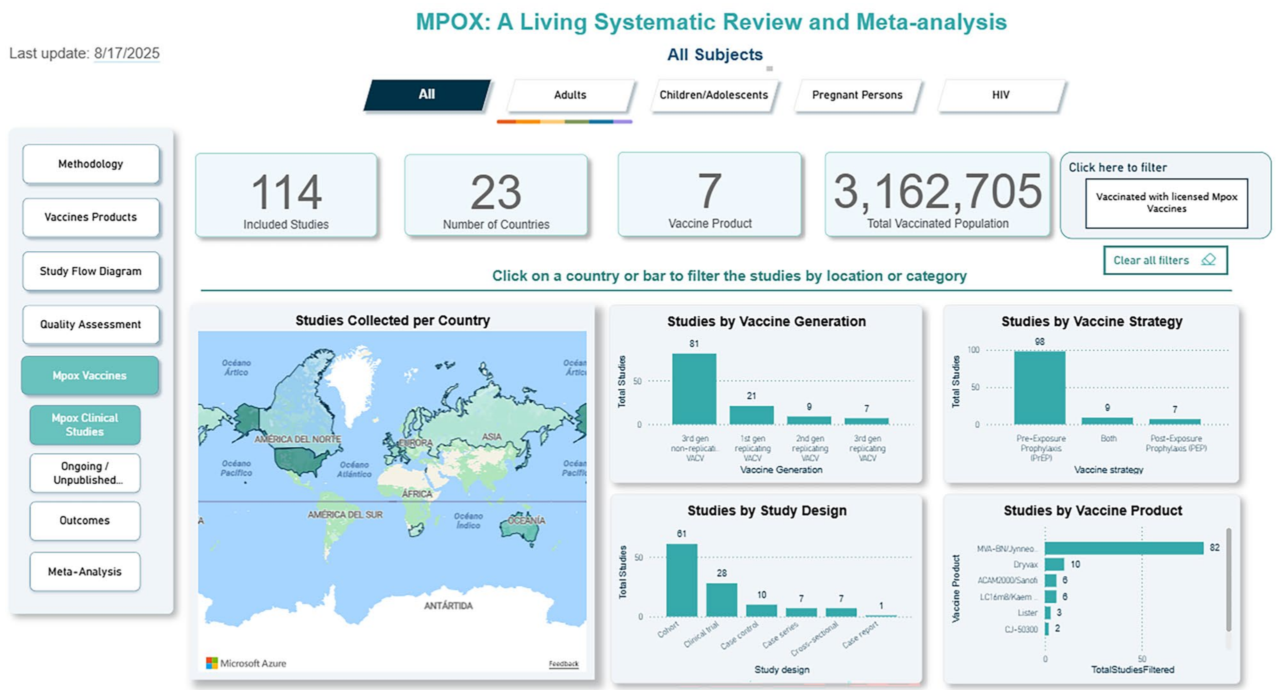

Fig. 2 Clinical evidence dashboard: vaccinia-based vaccines studies informing Mpox vaccine use

Table 3 Summary of findings of maternal pregnancy-related outcomes and safety neonatal outcomes (vaccinated pregnant persons vs unvaccinated pregnant persons)

Outcome	Vaccine generation	RR (95% CI)	Unvaccinated vs vaccinated/1000 persons[a]	Studies (*n*)	GRADE Certainty of Evidence
Congenital anomalies	First	1.25 (1.01–1.54)	31 vs 39 (+8)	9	Very low
Low birth weight	First	2.00 (0.18–21.86)	4 vs 8 (+4)	1	Very low
Neonatal death	First	1.69 (0.38–7.48)	8 vs 14 (+6)	2	Very low
Preterm birth	First	1.08 (0.78–1.50)	64 vs 69 (+5)	2	Very low
Preterm birth extremely	First	0.88 (0.36–2.15)	8 vs 7 (−1)	1	Very low
Spontaneous abortion	First	1.02 (0.70–1.48)	12 vs 12 (0)	8	Very low
Stillbirth	First	1.02 (0.70–1.48)	14 vs 22 (+8)	3	Very low

CI confidence interval, *RR* risk ratio

[a]Vaccinated—vaccinated difference/1000 persons

3.2.2 Neonatal Outcomes

Data on neonatal outcomes following maternal vaccination were available only for first-generation replicating VACV. In a pairwise meta-analysis, vaccination during pregnancy compared with no vaccination was associated with an RR of 1.25 (95% CI 1.01–1.54; $I^2 = 0\%$; nine studies, including 92,751 pregnant persons, of whom 8834 were vaccinated) for congenital anomalies (Fig. 3). Across the studies reporting congenital malformations following maternal vaccination with first-generation smallpox vaccines, most did not identify any birth defects, with several cohorts from South Africa, the USA, Poland, and Iran reporting no malformations (Table S8 of the ESM). However, some studies documented a range of congenital anomalies, including hydrocephalus, spina bifida, cleft palate, Down syndrome, congenital heart disease, and musculoskeletal malformations. Notably, Greenberg and Yankauer Jr [62] reported a broad spectrum of anomalies, such as microcephaly, imperforate anus, polycystic kidneys, absent or supernumerary digits, and hemangiomas. Ryan et al. [60, 63] described cardiac defects (atrial and ventricular septal defects, pulmonary valve abnormalities), gastrointestinal malformations (gastroschisis, omphalocele), and musculoskeletal anomalies. A single study involving a third-generation vaccine (MVA-BN)

Table 4 Proportional meta-analysis of neonatal outcomes following maternal mpox and vaccinia-based smallpox vaccination and background rates

Outcomes	Vaccine generation	Vaccina-ted (*N*)	Days to outcome	Studies (*n*)[a]	Events per 100 vaccinated persons (95% CI)	I^2	Background rates [56] (95% CI)
Congenital anomalies	First	9742	NR	14	2.52 (1.55–3.68)	82%	Global: 5–6% HICs: 4.70% LMICs: 6.50%
Low birth weight	First	655	NR	3	4.02 (1.09–8.51)	79%	Global: 14.7% (13.7–16.1) HICs: 8.52% LMICs: 13.7% (12.40–15.4)
Neonatal death	First	863	NR	3	1.28 (0.55–2.24)	0%	Global: 1.8% (1.7–1.9) HICs: 0.33% (0.31–0.35) LMICs: 2.7% (23.97–31.41)
Preterm birth[b]	First	5605	NR	6	6.28 (5.63–6.97)	28%	Global: 10.6% (9–12) HICs: 11.2% (9.50–13.20) LMICs: 15.4% (10.6–19.1)
Extremely preterm birth[c]	First	882	NR	1	0.57 (0.18–1.32)	–	Global: 0.5% HICs: 0.64% LMICs: 0.90%
Fetal vaccina	First	551	NR	2	0.00 (0.00–0.32)	0%	Not available
Stillbirth	First	1943	NR	9	2.95 (1.59–4.65)	65%	Global: 1.39 % HICs: 0.34 % LMICs: 2.27 %

CI confidence interval, *HICs* high-income countries, *LMICs* low- to middle-income countries, *NR*

[a]Disaggregated data (i.e., subpopulations) from the same study were meta-analyzed under the same ID and counted individual studies

[b]< 37 weeks of gestational age

[c]< 28 weeks of gestational age

reported anencephaly in a case of inadvertent vaccination during early pregnancy [64].

Overall, most studies did not report higher rates of congenital anomalies compared with unvaccinated controls; however, the pooled estimate suggested a small increase considered very uncertain because of imprecision and heterogeneity. In the sensitivity analysis excluding studies of poor quality for this outcome, the RR was 1.22 (95% CI 0.95–1.57; $I^2 = 0\%$; three studies, 5054 vaccinated persons). For low birth weight, the RR was 2.00 (95% CI 0.18–21.86; one study, 112 vaccinated pregnant persons). Neonatal death showed an RR of 1.69 (95% CI 0.38–7.48; $I^2 = 77\%$; two studies, 794 vaccinated pregnant persons). Preterm birth was not significantly associated with vaccination (RR 1.08, 95% CI 0.78–1.50; $I^2 = 77\%$; two studies, 5054 vaccinated pregnant persons), while extremely preterm birth (< 28 weeks) had a RR of 0.88 (95% CI 0.36–2.15; one study, 882 vaccinated pregnant persons). For low birth weight, neonatal death, preterm birth, extremely preterm birth, spontaneous abortion, and stillbirth, no sensitivity analysis by risk of bias could be performed, as the studies are all at the same risk of bias level (the certainty of evidence and the absolute effect are presented in Table 3).

In proportional meta-analyses (Table 4), we found that congenital anomalies occurred in a proportion of 2.52 per 100 vaccinated pregnant persons (95% CI 1.55–3.68; $I^2 = 82\%$; 14 studies, 9742 pregnancies), low birth weight occurred in 4.02 per 100 vaccinated pregnant persons (95% CI 1.09–8.51; $I^2 = 79\%$; three studies, 655 vaccinated pregnant persons), for neonatal death the proportion was 1.28 per 100 vaccinated pregnant persons (95% CI 0.55–2.24; $I^2 = 0\%$; three studies, 863 vaccinated pregnant persons), for preterm birth 6.28 per 100 vaccinated pregnant persons (95% CI 5.63–6.97; $I^2 = 28\%$; six studies, 5,605 vaccinated pregnant persons), and for extremely preterm birth 0.57 per 100 vaccinated pregnant persons (95% CI 0.18–1.32; one study, 882 vaccinated pregnant persons). Two studies (551 vaccinated pregnant persons) found no cases of fetal vaccinia (0.00 per 100; 95% CI 0.00–0.32; $I^2 = 0\%$) (Table 4). Lane et al. reported that between 1932 and 1971, 49 cases of fetal vaccinia had been documented. In nearly all instances, the mothers had received a primary smallpox vaccination or exhibited a primary-type reaction (i.e., the characteristic local "take" after first-time vaccination with a replicating vaccinia vaccine), accompanied by systemic symptoms. The gestational age at vaccination ranged from 3 to 24 weeks, and delivery typically occurred within 3–13 days after vaccination. Almost all affected fetuses were stillborn or died shortly after birth [65]. Three additional cases were reported in the USA up to 1978 [66]. We did not include these data

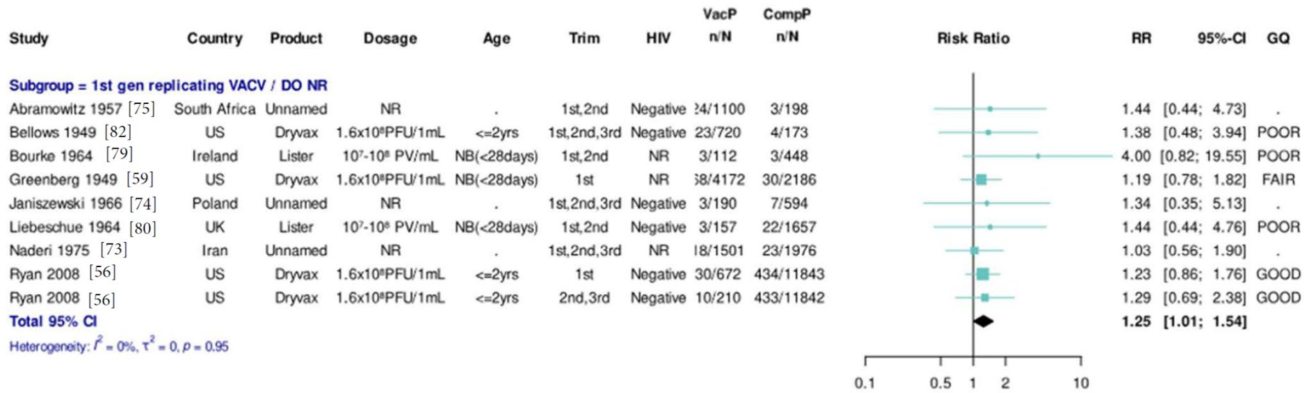

Fig. 3 Pairwise meta-analysis comparing one dose of a first-generation vaccination with an inactive arm or placebo for congenital anomalies*. *CI* confidence interval, *CompP n/N* total events/total population in comparator population, *DO* days since vaccination to outcome measure, *GQ* Global Quality assessment, *N* total patients, *NR* not reported, *RR* relative risk, *Trim* trimester of mother vaccination, *VacP n/N* total events/total population in vaccinated population. *HIV status negative/not reported; smallpox vaccination status: unvaccinated; Mpox clade, gender, route of administration, transgender women, occupational exposure risk: not reported

in the meta-analysis because there was no clear number of vaccinated pregnant persons.

We also performed proportional meta-analyses to summarize frequencies from one-sample studies and conducted targeted searches for background rates of each maternal-infant event, which we previously published. These global high-income countries and low- and middle-income countries rates provide essential reference points for contextualizing our findings [56]. All outcomes were below the background rates, except for neonatal death and stillbirth, which were higher than the background rates observed in high-income countries (Table 4). The available data allowed for a sensitivity analysis by excluding poor-quality studies, specifically those related to congenital anomalies, low birth weight, and preterm birth, which presented a slightly higher proportion of events (for more detailed information, see Table S8 of the ESM).

3.3 Safety of mpox and Historical Smallpox Vaccines Administered During Childhood and Adolescence

For these outcomes, we were unable to perform a pairwise meta-analysis because of a lack of data from comparative studies in this population. In this section, we present the results of proportional meta-analyses. For first-generation vaccines, the estimated proportion of encephalitis was 0.00 (95% CI 0.00–0.00; $I^2 = 91\%$) based on two sub-studies, including 1,175,000 vaccinated children. One study reported only one related death out of 650,000 vaccinated children and one case of eczema vaccinatum among 558,000 vaccinated children [67]. Generalized vaccinia occurred at a rate of 0.01 per 100 vaccinated individuals (95% CI 0.00–0.04; $I^2 = 99\%$), according to two sub-studies that included 1,175,000 children (for detailed results, see Table 5). For the third-generation vaccine (LC16m8), the proportion found for encephalitis was 0.24 per 100 vaccinated individuals (95% CI 0.10–0.44, $I^2 = 86\%$) in two sub-studies [68] among 100,340 vaccinated children.

Only Ladhani et al. [9] reported reactogenicity outcomes after post-exposure prophylaxis during the 2023 mpox outbreak. The study described 87 children and adolescents in the UK who received a single dose of MVA-BN (third-generation vaccine) as post-exposure prophylaxis within 2 weeks of close contact with a confirmed mpox case. It also reports the following adverse events among vaccinated individuals: pain or swelling 40% (95% CI 25.70–55.67), rash 8.89% (95% CI 2.48–21.22), fever or headache 4.44% (95% CI 0.54–15.15), and myalgia and nausea each affected 2.22% (95% CI 0.06–11.77).

3.4 Effectiveness Outcomes

3.4.1 Pregnant Persons

No clinical studies specifically reported VE estimates for pregnant persons.

3.4.2 Children and Adolescents

Pediatric VE data were limited to a single UK observational study Ladhani et al. [9], during the 2022–23 outbreak. Single-dose MVA-BN given as post-exposure prophylaxis to children and adolescents resulted in no confirmed mpox infections within 28 days of vaccination. The studies included insufficient sample sizes to generate precise VE

Table 5 Proportional meta-analysis of children's safety outcomes smallpox vaccination

Outcomes	Vaccine generation	Vaccinated (*N*)	Days to outcome	Studies (*n*)[a]	Events per 100 vaccinated persons (95% CI)	I^2
Eczema vaccinatum	First	558,000	NR	1	0.00 (0.00–0.00)	–
	Second: ACAM	254	0–30	4	0.00 (0.00–0.64)	0%
Encephalitis	First	1,175,000	NR	2	0.00 (0.00–0.00)	91%
	Second: ACAM	11,079	0–30	5	0.00 (0.00–0.64)	0%
	Third: LC16m8	100,340	NR	2	0.24 (0.10–0.44)	86%
Fever	Second: ACAM	11,129	0–30	4	7.49 (2.68–14.22)	93%
	Third: MVA-BN	45	0–30	1	4.44 (0.54–15.15)	–
	Third: LC16m8	100,340	NR	1	0.00 (0.00–0.01)	–
Generalized vaccinia	First	1,175,000	NR	2	0.01 (0.00–0.04)	99%
	Second: ACAM	254	0–30	4	0.00 (0.00–0.64)	0%
Headache	Second: ACAM	11,129	0–30	5	38.71 (16.87–63.19)	99%
	Third: MVA-BN	45	0–30	1	4.44 (0.54–15.15)	–
Inadvertent inoculation	First	558,000	NR	1	0.01 (0.00–0.01)	–
Myalgia	Second: ACAM	11,129	0–30	5	31.41 (10.27–57.60)	99%
	Third: MVA-BN	45	0–30	1	2.22 (0.06–11.77)	–
Nausea	Second: ACAM	11,129	0–30	5	13.31 (4.06–26.49)	97%
	Third: MVA-BN	45	0–30	1	2.22 (0.06–11.77)	–
Pain	Second: ACAM	11,129	0–30	5	42.09 (15.38–71.54)	99%
	Third: MVA-BN	45	0–30	1	40.00 (25.70-–5.67)	–
Rash	Second: ACAM	11,129	0–30	5	6.57 (1.65–14.03)	95%
	Third: MVA-BN	45	0–30	1	8.89 (2.48–21.22)	–
	Third: LC16	100,340	NR	1	0.08 (0.06–0.10)	–
Swelling	Second: ACAM	254	0–30	4	6.44 (3.82–9.63)	0%
	Third: MVA-BN	45	0–30	1	40.00 (25.70–55.67)	–
Product-related death	Second: ACAM	254	0–30	4	0.00 (0.00–0.64)	0%
	First	650,000	NR	1	0.00 (0.00–0.64)	–

CI confidence interval, *NR*

[a]Disaggregated data (i.e., subpopulations) from the same study were meta-analyzed under the same ID and counted individual studies

estimates, and researchers identified a lack of pediatric data on hospitalization or mortality.

4 Discussion

4.1 Main Findings

This LSR is the most comprehensive synthesis to date of vaccinia-based vaccines, historically developed for smallpox (first and second generation) and those used for mpox prevention (third and fourth generation) in pregnant persons, children, and adolescents. The body of available evidence included in this review relates almost entirely to pre-exposure vaccination, with the exception of a single post-exposure study, which was analyzed and reported separately because of its distinct context and objectives. Because no clinical trials have directly evaluated vaccines for mpox prevention in these groups, our findings are based only on observational studies and largely derived from the historical use of first-generation smallpox vaccines during smallpox eradication campaigns, including the 2022–23 outbreak of mpox. Therefore, the certainty of evidence was considered as very low because of study design limitations, indirectness, and heterogeneity.

The evidence on congenital malformations following maternal smallpox vaccination is limited and heterogeneous, making it difficult to draw definitive conclusions about potential teratogenic effects. Although the pooled estimate suggested an increased risk of congenital anomalies among vaccinated pregnant individuals, this finding should be interpreted with caution. The CI was wide and the lower bound was close to the null value, indicating substantial statistical uncertainty and limited precision. Moreover, the evidence is largely derived from historical observational studies with inherent methodological limitations. Most cohort studies, including those conducted in different regions and with various first-generation vaccine strains did not report higher rates of congenital anomalies compared with unvaccinated controls, suggesting that maternal vaccination may not be associated with a substantial increase in the overall risk of birth defects. However, isolated reports documented a broad spectrum of anomalies, which ranged from neural tube defects and congenital heart disease to musculoskeletal and gastrointestinal malformations. These findings, often based on small sample sizes and historical data collected before the establishment of standardized surveillance systems, should be interpreted with caution. The single case of anencephaly reported after inadvertent exposure to a third-generation vaccine further highlights the need for careful monitoring. However, causality cannot be established from individual case reports. Overall, while the available evidence does not indicate a clear teratogenic signal, gaps in data quality and methodological limitations underscore the importance of robust prospective studies to better assess the safety of maternal vaccination during pregnancy.

Most proportional estimates generally fell below the background population rates¸ or at most within their corresponding CIs. Given the variability in background rates across populations and time periods, proportion meta-analyses were used descriptively to summarize event frequencies, with background rates provided for contextual interpretation only and without implying comparative or causal inference In children, serious adverse events following smallpox vaccination were rare, and early data on MVA-BN use as post-exposure prophylaxis reported only mild self-limiting reactions. No study reported direct effectiveness estimates in pregnancy, and pediatric data were limited to a single small UK cohort [9].

Our LSR found no evidence of an increased risk of significant adverse pregnancy outcomes following vaccination with vaccinia-based vaccines, aligning with the conclusions of Badell et al. [59], and other historical analyses of smallpox vaccination in pregnancy [69]. Some studies in our LSR suggested a modest signal for congenital anomalies with associated first-generation smallpox vaccines; however, there are no data regarding the more recent third-generation vaccines. It is estimated that one case of fetal vaccinia might occur for every 10,000–100,000 pregnant persons who receive the smallpox vaccine for the first time [70]. That may explain the zero event observed among 551 vaccinated pregnant persons in two more recent cohorts, reflecting the rarity of the event [63, 71]. This descriptive finding, highlights the rarity of the outcome and the limited exposure population, and does not provide a precise or definitive estimate of risk. Proposed risk factors for fetal vaccinia include primary vaccination with replication-competent vaccinia vaccines, systemic symptoms following vaccination, and potential host susceptibility factors such as unrecognized immunocompromise; however, evidence remains extremely limited [59]. It is important to note that the effect of replicating first-generation vaccines should not be extrapolated to the non-replicating vaccines for this outcome.

In children, historical data on smallpox vaccines indicated very low rates of serious adverse events [72]. Recent evidence from the outbreak era for MVA-BN in pediatric contacts shows a safety profile characterized by mild, self-limiting local or systemic reactions [9]. Nevertheless, safety data specific to children and adolescents remain scarce. Although several studies reported including participants from these age groups, outcomes were rarely disaggregated or described in detail. Early results from an National Institutes of Health/National Institute of Allergy and Infectious Diseases-sponsored trial in adolescents aged 12–17 years showed immune responses and safety profiles comparable to adults after two standard doses of MVA-BN, supporting recent regulatory extensions to this age group [73].

No clinical studies reported mpox vaccines' VE estimates for pregnant persons. This absence of direct efficacy and effectiveness evidence represents a critical gap for our population of interest, and interpretation for this group must rely on indirect data from the general population during historical smallpox vaccination campaigns [74]. The estimated VE following two vaccine doses of MVA-BN to this population ranged from 66 to 90% [75]. Pediatric effectiveness data remain minimal, limited to a single post-exposure prophylaxis cohort in the UK, which reported no cases within 28 days [9]. Our interactive hub, Safe in Pregnancy Safe in Children, presents updated data on the general population that helps as indirect evidence for recommendations for these special populations (https://www.safeinpregnancy.org). Two studies reported effectiveness estimates in adults, derived from multiple observational studies conducted during the 2022–23 mpox outbreak, indicating that MVA-BN provides moderate-to-high protection against mpox infection and hospitalization, with greater and more durable protection following two doses [26, 75]. A phase III open-label trial of a two-dose MVA-BN vaccine in pregnant and postpartum individuals, as well as in children up to 24 months of age, is underway and scheduled to conclude in July 2027 [76].

4.2 Strengths

A key strength of our study is its LSR design, which enables continuous surveillance and the rapid incorporation of new evidence, in accordance with WHO and Cochrane LSR standards [34, 36]. The comprehensive search strategy, spanning peer-reviewed, preprint, and gray literature sources without time or language restrictions, minimizes publication and language bias, which is crucial for historical smallpox data and recent mpox studies [9, 59, 67, 72].

We contextualize contemporary MVA-BN safety and effectiveness findings against decades of real-world use in pregnant persons and children by integrating historical and modern vaccinia-based vaccine data within a single analytic framework. Methodological rigor and transparent dissemination via an interactive dashboard further strengthen the reliability and policy relevance of our conclusions.

4.3 Limitations

Despite including regulatory agency sources and gray literature, pharmacovigilance data from low- and middle-income countries may be under-represented or less accessible, potentially affecting the generalizability of our findings and limiting conclusions in equity-relevant contexts. The principal limitation of this review is the scarcity of direct evidence on mpox vaccination in pregnant persons, infants, children, and adolescents. Most maternal safety data were derived from historical use of first-generation replicating vaccinia-based smallpox vaccines, administered under markedly different epidemiological contexts and surveillance standards. Extrapolating these data to modern non-replicating platforms such as MVA-BN relies mainly on indirect evidence. Indirectness, in addition to imprecision, further reduces the certainty of the body of evidence. Additionally, only one study reported data on post-exposure prophylaxis.

Another limitation is the absence of randomized controlled trials, as well as the low quality of historical evidence, which is marred by methodological issues such as incomplete outcome ascertainment and limited control for confounding, potentially biasing risk estimates. For pediatric populations, contemporary safety data remain sparse. In addition, heterogeneity in study design, outcome definitions, and follow-up periods prevented the performance of meta-analysis for several endpoints and limited the precision of pooled estimates. Publication and reporting bias are possible, particularly for rare adverse events that may have been underreported in historical and modern studies.

4.4 Implications for Practice and Research

Our findings have several implications for clinical practice, health decision making, and research agendas. Considering the scarcity of direct evidence on pregnant persons and children, current recommendations rely mainly on indirect evidence from non-pregnant adults and historical smallpox vaccination. Generalizability is limited by variability in surveillance capacity and healthcare systems across settings, with most evidence originating from high-income countries and historical programs. Policy decisions should distinguish between pre- and post-exposure vaccination contexts and prioritize strengthened pharmacovigilance, including pregnancy and pediatric surveillance, particularly as vaccine use expands to new populations and regions. This evidence gap highlights the urgent need for high-quality studies that specifically target these populations.

The WHO recommends that, during pregnancy, where consideration is given to vaccination, a non-replicating vaccine (MVA-BN) may be used. Administration of MVA-BN in pregnancy constitutes "off-label" use.

There are no data available to assess the risk of minimally replicating (LC16-KMB) vaccines in pregnant persons. No development and reproductive toxicology studies have been performed.

Replicating vaccine (such as ACAM2000) should not be used in pregnancy. Our LSR reinforces available evidence that suggests the cautious use of third-generation non-replicating vaccines, such as MVA-BN, in scenarios of high exposure risk, such as extended outbreaks. Considering the favorable safety profile in the general adult population and the absence of safety issues in historical data with smallpox vaccines, vaccination could be considered in targeted outbreaks, accompanied by clear and shared decision making that acknowledges these uncertainties. Key priorities for future research include: (i) randomized trials or prospective observational studies with an adequate follow-up to assess safety, effectiveness, and immunogenicity in pregnant persons, children, and adolescents and (ii) enhanced post-marketing active pharmacovigilance in these special populations to detect adverse events.

5 Conclusions

The available evidence, which is predominantly historical and indirect, suggests no consistent signal of increased adverse outcomes following vaccinia-based vaccination in pregnancy or childhood; nevertheless, uncertainty remains substantial, particularly for contemporary vaccines. High-quality prospective studies and strengthened pharmacovigilance are urgently needed. Our LSR adds value beyond previous reviews by integrating modern non-replicating vaccine data into the historical safety evidence base and adopting a living approach that allows near-real-time updates as new maternal and pediatric data emerge. This approach holds relevance for emerging pathogens, as policymakers must make decisions before robust direct evidence becomes available.

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Declarations

Conflicts of Interest/Competing Interests Agustín Ciapponi, Jamile Ballivian, Mabel Berrueta, Juan M. Sambade, Noelia Castellana, Ariel Bardach, Martin Brizuela, Julieta Caravario, Daniel Comande, Esteban Couto, Agustina Mazzoni, Edward Parker, Florencia Salva, Katharina Stegelmann, Xu Xiong, Andy Stergachis, Flor M. Munoz, and Pierre Buekens have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval Ethics approval was not required because this study is a systematic review involving no original data collection or human subjects.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material All data are available in https://www.safeinpregnancy.org/#mpox.

Code Availability Not applicable.

Authors' Contributions Conceptualization: MBe, AC, JB, JMS, AM, AB, MBr, DC, NC, EPKP, AS, XX, FMM, PB. Methodology: MBe, AC, JB, JMS, AM, AB, MBr, DC, NC, EPKP, AS, XX, FMM, PB. Software and visualization: NC, MBe. Validation and data curation: JB, MBe, JMS, JC, EC, MBr. Formal analysis: MB, JB, AC, JMS. Investigation (screening/extraction/risk of bias): JB, JC, FS, MBr, JMS, KS, AM, EC, DC. Resources and funding acquisition: MBe, AC, PB, FMM, AS, XX, EPKP. Writing (original draft): AC, MBe, JB. Writing (review and editing): MBe, AC, JB, JMS, EC, KS, AM, JB, MBr, DC, NC, EPKP, AS, XX, FMM, PMB. Supervision: AC, MBe, EPKP, AS, XX, FMM, PMB. Project administration: JB, MBe. All authors read and approved the final manuscript.

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