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Systematic Review

Mpox varicella-zoster virus coinfection in the Democratic Republic of Congo: a systematic review and meta-analysis

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Abstract

Introduction: Monkeypox (Mpox) is an endemic disease in the Democratic Republic of Congo (DRC). After five decades of outbreaks, gaps still remain in understanding clinical patterns and coinfections with varicella-zoster virus (VZV) and human immunodeficiency virus (HIV) in this high-burden setting. This systematic review and meta-analysis were conducted to synthesize data on Mpox clinical presentation and coinfection trends in the Democratic Republic of the Congo. Estimating the burden of VZV and HIV coinfections will help informing decision maker during the fight against this outbreak.

Methods: This study was conducted by systematically extracting data from online databases including PubMed, ScienceDirect, and Google Scholar. The pooled estimate VZV and HIV coinfection rates were calculated using fixed and random-effects models. Subgroup analyses were performed by time period, region, study design, setting, and participant characteristics.

Results Among a total of 1,841 confirmed Mpox cases, VZV coinfection was 9.69% (95% CI: 1.33–18.06; n = 8), with higher rates in Kivu (33.33%) compared to Equateur (11.10%). The VZV pooled prevalence rate among 64,131 suspected Mpox cases was 16.73% (95% CI: 5.36-28.10; n = 8), with $I^2 = 99.4\%$ ($p < 0.001$). The pooled estimate of HIV coinfection rate was low (0.52%, 95% CI: 0.18–0.87) at national level but elevated in South Kivu (1.64%). Among confirmed cases, rash (99.97%), painful lesions (78.17%), and Malaise (77.14%) were the main clinical presentation and this highlights their diagnostic importance in the case definition. A similar clinical pattern of Mpox was observed among suspected cases, were almost all recorded cases reported rash (99.43%) and fever (98.91%). Heterogeneity was high ($I^2 > 90\%$) for most study outcomes.

Conclusion: The substantial VZV coinfection prevalence and distinct regional HIV patterns highlight critical gaps in syndromic surveillance and the urgent need for integrated diagnostic strategies. This review confirms that Mpox in the DRC presents with near-universal rash, underlining their centrality to case definitions. These findings provide essential evidence for strengthening frontline detection and tailored outbreak response in endemic zones.

Keywords: monkeypox; varicella-zoster virus; HIV patterns; clinical manifestation; simian orthopoxvirus

Introduction

The Simian Orthopoxvirus, which causes monkeypox (Mpox), has become a serious public health concern, especially in endemic areas of Central and West Africa [1,2]. The Democratic Republic of Congo (DRC) remains the epicenter of human Mpox cases, where it has been responsible for 4.18% mortality (95% CI: 0.29-8.08) among confirmed cases since the first case was discovered in 1970 [3]. The Mpox virus belongs to the Orthopoxvirus genus (the same genus as the smallpox virus or variola virus). Scientists have identified two main types (clades) of the Mpox virus: Clade I (previously called the Congo Basin clade) and Clade II (previously called the West African clade). Clade I, which is common in the DRC, tends to cause more severe illness, has a higher mortality rate (up to 10%), and spreads more easily than Clade II. The recent global spread of a subtype of Clade II (Clade IIb) in 2022-2023, largely through sexual contact between people, demonstrated the virus's ability to cause widespread outbreaks [4,5]. However, in the DRC, Mpox mainly spreads from animals to humans, with occasional human outbreaks linked to animals like rodents and other small mammals [6,7] .

The clinical presentation of Mpox often resembles that of smallpox, though typically less severe. Classic symptoms include fever, lymphadenopathy, and a characteristic vesiculopustular rash that progresses through macular, papular, vesicular, and pustular stages before crusting over [8,9]. Nonetheless, notable differences have been documented in clinical presentations between several outbreaks and demographic settings [4,10–14]. Accurate clinical diagnosis is hampered by this variability, especially in settings with limited resources when test confirmation might not be available [15]. The situation is further complicated by the co-circulation of varicella-zoster virus (VZV), Mpox cases may be misdiagnosed and underreported due to the co-circulation of varicella-zoster virus (VZV), which causes comparable cutaneous clinical presentation [10,16,17]. Up to 40% of suspected Mpox cases in the DRC may actually be VZV infections, according to study report, highlighting the urgent need for enhanced diagnostic capabilities in endemic areas [4].

The epidemiological context has become more complex due to the existence of human immune deficiency virus (HIV) as a comorbidity among some Mpox patients [18,19]. Commercial sex work along transit routes, frequent cross-border migration, and widespread connection all contribute to the regional spread of infectious diseases like HIV and Mpox [20]. According to preliminary data, HIV-Mpox coinfection rates in this endemic context are significantly lower (<4%), which may reflect different transmission dynamics [6]. Although it is unclear how HIV affects the immune response among people affected by Clade I Mpox, the coinfection is more likely to favor disease severity and the patient may die if they do not receive the proper medical care [19,21].In addition, significant obstacles to optimal surveillance and case reporting in DRC are created by insufficient healthcare infrastructure, persistent violence in eastern regions, and restricted access to diagnostics [3,15].

Even though Mpox disease has been common in the DRC for more than 50 years, there are still significant gaps in our knowledge regarding the disease's epidemiology. Reliable burden estimation and outbreak response have been hampered by uneven diagnostic methods, a lack of established case criteria, as well as genetic surveillance. However, new tools provided by recent developments in molecular diagnostics, such as multiplex polymerase chain reaction (PCR) assays, are used to enhance case detection are, that can distinguish Mpox from VZV [10]. However, in the majority of this country, these advanced diagnostic instruments are frequently still unavailable [22]. These difficulties may lead to a delayed diagnosis, insufficient treatment, and a higher Mpox death rate [23]. Furthermore, the 2022 global outbreak highlights the possibility of Mpox virus adaptation to human-to-human transmission, underscoring the need for increased surveillance in endemic areas to identify any changes in clinical presentation or transmission patterns [24].

It is necessary to produce updated findings on the clinical and paraclinical presentation of the disease in order to support the development of more precise case definitions specific to the DRC context and to provide evidence to direct clinical management and public health interventions in this high burden setting. The study is particularly timely given the recent increase of Mpox vaccination trials in endemic countries and the requirement for data-driven strategies to optimize their deployment [25–28]. The aim of this systematic review and meta-analysis was to compile data on Mpox clinical presentation and coinfection trends in the Democratic Republic of the Congo from 1970 to 2024. We attempted to estimate the burden of VZV and HIV coinfections by examining data from confirmed mpox cases.

Methods

Study design

This systematic review and meta-analysis assessed the clinical presentation and co-infection patterns of Mpox cases in the DRC. The Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines was followed while reporting the study [29].

Operational definition

A suspected Mpox case was defined as an individual presenting with a vesicular or pustular rash characterized by deep-seated, firm pustules, and at least one of the following: fever preceding the rash, lymphadenopathy (inguinal, axillary, or cervical), or pustules or crusts on the palms or soles. A case was considered laboratory-confirmed Mpox if at least one specimen tested positive for *Orthopoxvirus* using a specific assay or Mpox-specific real-time PCR, or if Mpox was isolated in culture. A case was defined as laboratory-confirmed VZV if at least one specimen yielded a positive result in a real-time PCR assay targeting the VZV-specific DNA signature [10]. Similarly, a case was defined as laboratory-confirmed HIV if at least one specimen showed a positive result in an HIV antigen-specific assay or HIV-specific real-time PCR [5,30].

Eligibility criteria

Observational studies reporting Mpox clinical symptoms and VZV coinfection in the DRC were included in this systematic review and meta-analysis. During the screening process, we eliminated duplicate publications and omitted studies with ambiguous result definitions. There were no publication date limits, but only original research articles written in English and French were included.

Article searching strategy

PubMed, ScienceDirect, and Google Scholar were systematically searched to identify eligible published records. The search strategy included looking through titles and abstracts using a combination of keywords and Medical Subject Headings (MeSH). Boolean operators ("AND" and "OR") were used to refine the search, with terms like (monkeypox) OR (monkeypox virus) OR (human monkeypox) OR (Mpox) OR (mpox) OR (MPX) OR (epidemiology) OR (severe) AND (DRC) OR (Democratic Republic of Congo) OR (Zaire) (Supplementary file 1 and Supplementary Table 1). Additionally, a manual search for additional publications that were not indexed in these databases. The final search was concluded on February 27, 2025.

Data extraction

We developed a Microsoft Excel 2016 form to collect study characteristics from all included study reports. This form captured the first author's name, study year, region, study design, study type, type of participant, setting, number of confirmed VZV cases, frequency of each clinical manifestation, and the number of suspected and confirmed Mpox cases. Two authors independently assessed the relevance and quality of each article. Any disagreements between the reviewers were resolved through discussion with a third author to reach a consensus

Data quality assessment

The Joanna Briggs Institute (JBI) quality assessment tool was used to evaluate the quality of studies included [31]. Risk of bias was assessed using nine or ten criteria, depending on the study design. (1) For cross-sectional studies, criteria included: appropriateness of the sampling frame, use of a suitable sampling technique, adequate sample size, description of study subjects and setting, sufficient data analysis, use of valid methods for identifying conditions and measurements, use of appropriate statistical analysis, and an adequate response rate (≥60%). (2) For case series, criteria included: standardized measurement and valid identification of the condition for all participants, consecutive and complete inclusion of participants, reporting of participant demographics and clinical information, reporting of outcomes or follow-up results, reporting of the presenting site(s)/clinic(s) demographic information, and statistical analysis appropriate for case series studies. Each criterion was scored as 1 (yes) or 0 (no or unclear). The overall risk of bias was categorized as low (>50%), moderate (>25-50%), or high (≤25%).

Outcome measurement

The primary outcomes of this systematic review and meta-analysis were clinical manifestations of Mpox cases and the coinfection rate of VZV and Mpox. Secondary outcomes included the HIV and Mpox coinfection rate and the prevalence of VZV among suspected Mpox cases.

The VZV and Mpox coinfection rate was calculated by dividing the number of VZV and Mpox coinfected cases by the number of confirmed Mpox cases. Similarly, the HIV and Mpox coinfection rate was assessed by dividing the number of confirmed HIV and Mpox coinfected cases by the number of confirmed Mpox cases. The prevalence of VZV among suspected Mpox cases was calculated by dividing the number of confirmed VZV cases by the total number of suspected Mpox cases. For clinical features among suspected and confirmed Mpox cases, the proportion of each manifestation was determined by dividing its frequency by the number of suspected or confirmed Mpox cases, respectively.

Statistical analysis and synthesis

The heterogeneity between trials was evaluated using the I^2 statistic, which classified it as low (<25%), moderate (25-75%), or high (>75%). A random-effects model was used when heterogeneity was greater than 50%. Subgroup analyses were then carried out depending on study period, area, setting, participant type, study design, and disease burden. Furthermore, meta-regression explored whether study characteristics explained the variability in results. For the prevalence of VZV or HIV among suspected or confirmed Mpox cases, the time frames were defined based on major developments in healthcare systems: (1) 1970–1990: limited healthcare infrastructure in endemic regions; (2) 1991–2010: improvements in healthcare access and disease surveillance; (3) 2011–2024: strengthened global health initiatives and response systems [3]. Only study variables with meaningful and practical categories were included in the analyses. Univariable and multivariable meta-regression models were used to assess whether the pooled estimate varied according to the selected explanatory variable categories. Statistical significance was set at a p-value of <0.05. All analyses were performed using the 'meta' package in R Statistics version 4.4.2 [32].

Publication bias and sensitivity test

Publication bias was assessed visually using a funnel plot. The asymmetry of the inverted funnel shape suggested the potential of publication bias. The trim-and-fill method was used to adjust for potential missing studies [33]. To test the robustness of the findings we performed sensitivity analysis by iteratively excluding one study at a time and pooled the resulting estimate.

Results

A total of 157 records were found through the database search, and 4 additional reports were identified from other sources, for a total of 161 records. Nine duplicates were eliminated, and 152 distinct records were subjected to title and abstract screening before being evaluated for eligibility. Ultimately, 20 study reports met the inclusion criteria and were included in the meta-analysis (Fig. 1).

Studies selection

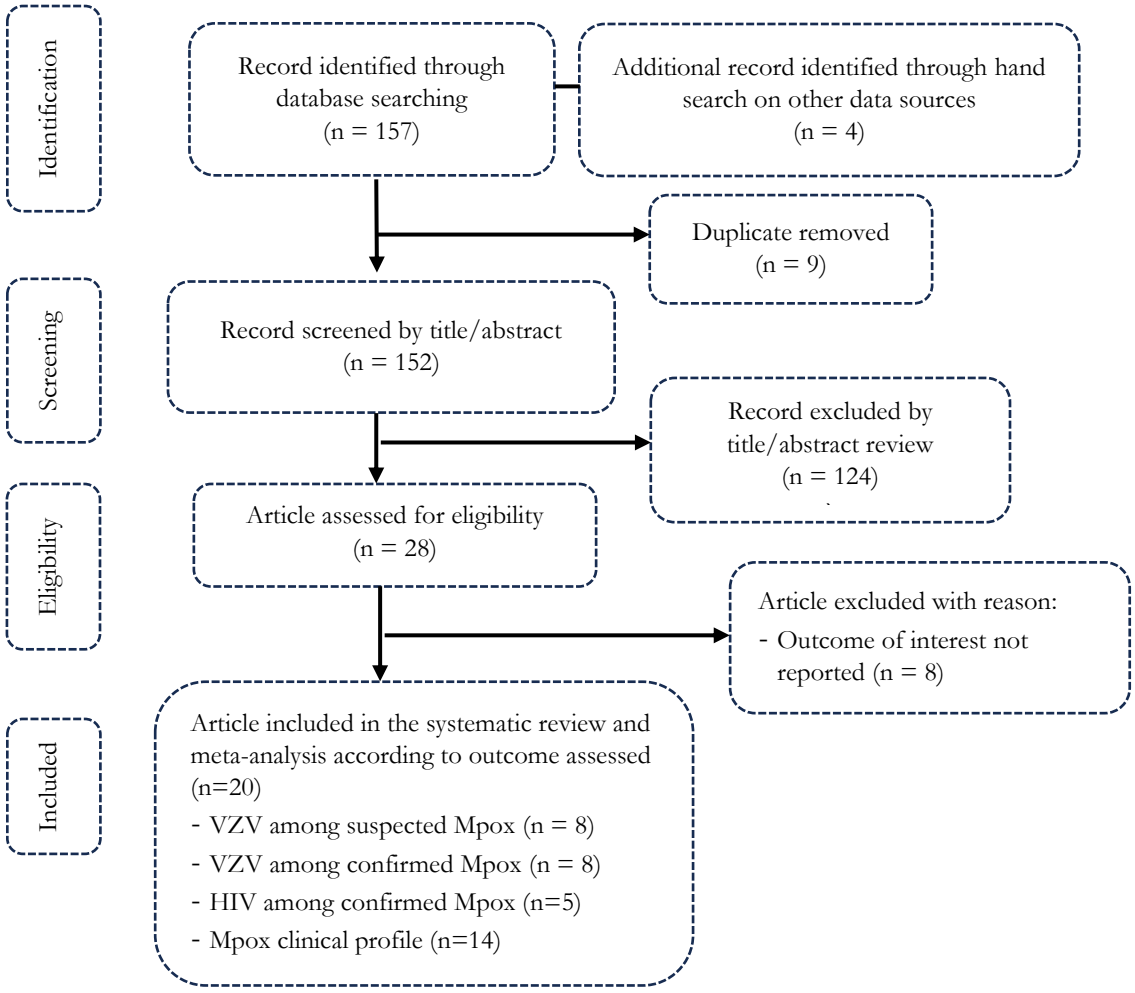

Fig. 1 PRISMA diagram flow of studies included in the meta-analysis

(VZV: Varicella-zoster virus; HIV: Human immunodeficiency virus)

Characteristics of studies included

Twenty studies, conducted between 1997 and 2024 in community and hospital settings across the DRC, were included in this comprehensive analysis. Data collection in most (n = 19) utilized surveillance and investigation,

targeting the general population and healthcare workers to describe VZV, HIV, and Mpox coinfection and the clinical features of suspected and confirmed Mpox cases (Table 1):

Table 1 Characteristic of studies assessing Mpox in DRC

Author	Study Year[1]	Region	Setting	Study population	Study type	Sampling	Risk of bias	Outcome of interest	VZV among confirmed Mpox case	HIV among confirmed Mpox case	Summary of findings
Jezek *et al.* [34]	1985	Nationwide	Community	General population	Surveillance and investigation report	Non-probabilistic	Low	Clinical feature	NR	NR	unvaccinated individuals, particularly young children, experienced an 11-15% case-fatality rate, while vaccinated individuals showed no deaths and altered disease presentation.
Hutin *et al.* [30]	1997	Sankuru	Community	General population	Surveillance and investigation report	Non-probabilistic	Low	Clinical feature	NR	Yes, *n*=0	This outbreak presented with notable attack and case-fatality rates. The cessation of smallpox vaccination in 1983, following global eradication, contributed to an increased population susceptibility to monkeypox.
Aplogan *et al.* [35]	1997	Kasai Oriental	Community	General population	Surveillance and investigation report	Non-probabilistic	Low	VZV coinfection	No	NR	There was a high prevalence of Mpox among children and a mix of primary and secondary transmission patterns across numerous villages. The outbreak was localized outbreaks and travel, close contact within households and neighborhoods facilitated the secondary case transmission.
Meyer *et al.* [36]	2001	Equateur	Community	General population	Surveillance and investigation report	Non-probabilistic	Low	VZV coinfection	Yes, *n*=2	NR	Two outbreaks were confirmed as monkeypox (4 deaths), two as co-infection of monkeypox and chickenpox (1 death), two as chickenpox (no deaths), and one outbreak yielded no viral evidence (no deaths).
Pittman *et al.* [12]	2022	Sankuru	Hospital	General population	Cross-sectional study	Non-probabilistic	Moderate	Clinical feature	NR	NR	Clinical course of Mpox in 216 PCR-confirmed cases revealed a 1.4% mortality rate and significant fetal loss in pregnant patients. Key findings included a high prevalence of rash and lymphadenopathy, with younger children exhibiting higher lesion counts and severe disease being associated with hypoalbuminemia and elevated viral load.
Nolen *et al.* [37]	2012	Tshuapa	Hospital	General population and healthcare worker	Surveillance and investigation report	Non-probabilistic	Low	VZV coinfection	Yes, *n*=0	NR	Half of possible cases were lab-confirmed monkeypox. 50% household attack rate, multiple family transmissions, and a mean 8-day incubation period (4-14 days) were observed.

Hughes *et al.* [11]	2014	Tshuapa	Community	General population	Surveillance and investigation report	Non-probabilistic	Low	VZV coinfection and Clinical feature	Yes, *n*=134	NR	A significant proportion of mpox cases were co-infected with VZV, exhibiting atypical clinical presentations and highlighting the complex interplay between these two viruses.
Petersen et al. [38]	2014	Tshuapa	Community	Healthcare worker	Surveillance and investigation report	Non-probabilistic	Low	VZV coinfection	Yes, *n*=1	NR	These findings suggest that while a smallpox vaccination scar may offer some protection against monkeypox, healthcare workers remain at risk of infection. The presence of co-infections further complicates the picture.
Osadebe *et al.* [4]	2014	Tshuapa	Community	General population	Surveillance and investigation report	Non-probabilistic	Low	VZV coinfection and Clinical feature	No	NR	Laboratory-confirmed Mpox and VZV cases presented with many of the same signs and symptoms, and the analysis here emphasized the utility of including 12 specific signs/symptoms when investigating Mpox cases
McCollum *et al.* [39]	2014	Kivu (North and South)	Community	General population	Surveillance and investigation report	Non-probabilistic	Low	VZV coinfection	Yes, *n*=1	NR	Report of the first confirmed cases of monkeypox (MPX) in forested areas of North and South Kivu Provinces, which aligns with ecological predictions for suitable Mpox transmission zones.
Whitehouse *et al.* [10]	2014	Tshuapa	Community	General population	Surveillance and investigation report	Non-probabilistic	Low	VZV coinfection and Clinical feature	Yes, *n*=169	Yes, *n*=4	Increased incidence compared to previous decades, likely due to waning smallpox immunity. While males generally had higher infection rates, females reported frequent contact with symptomatic individuals. Animal exposures were most common in males.
Mande *et al.* [40]	2019	Bas-Uélé	Community	General population	Surveillance and investigation report	Non-probabilistic	Low	VZV coinfection and Clinical feature	Yes, *n*=0	NR	Among 77 suspected cases, PCR revealed 27.3% monkeypox, 58.4% chickenpox, and 14.3% negative. Monkeypox cases showed distinct skin lesions.
Ngbolua *et al.* [41]	2019	North Ubangui	Hospital	General population	Surveillance and investigation report	Non-probabilistic	High	Clinical feature	NR	NR	Three cases of monkeypox in young males with similar clinical presentations, including fever, rash, itching, and abdominal pain. No case of death.
Kinganda-Lusamaki *et al.* [16]	2022	Nationwide	Community and Hospital	General population	Surveillance and investigation report	Non-probabilistic	Low	VZV coinfection and Clinical feature	Yes, *n*=0	NR	Adding antibody testing to PCR nearly doubled Mpox detection rates in the DRC (48% vs 34% with PCR alone), revealing hidden outbreaks across 14 additional health zones and proving current surveillance misses over 40% of cases.

Kibungu *et al.* [13]	2023	Kwango	Community	General population	Surveillance and investigation report	Non-probabilistic	Low	Clinical feature	NR	NR	A cluster of clades I monkeypox cases in the DRC shows sexual transmission, indicating this route is not limited to clade IIb.
Bangwen *et al.* [17]	2023	Nationwide	Community and Hospital	General population	Surveillance and investigation report	Non-probabilistic	Low	VZV coinfection	No	NR	There was a four-fold increase in incidence between 2010 and 2023, wider geographic spread, and high fatality rate in young children.
Brosius *et al.* [5]	2024	South Kivu	Hospital	General population	Cross-sectional study	Non-probabilistic	Moderate	Clinical feature	NR	Yes, *n*=6	Most suspected cases were PCR-positive for Mpox. Most cases reported contact with known Mpox, primarily spouses/partners in adults and family in children. Genital lesions were common in adults. Hospitalized mortality was low.
Mukadi-Bamuleka e*t al.* [14]	2024	North Kivu	Community	General population	Surveillance and investigation report	Non-probabilistic	Low	Clinical feature	NR	NR	Clade Ib monkeypox was introduced into North Kivu, including displacement camps, with suspected non-intimate contact transmission, affecting children.
Vakaniaki *et al.* [42]	2024	South Kivu	Community	General population	Surveillance and investigation report	Non-probabilistic	Low	Clinical feature	NR	Yes, *n*=3	The Mpox outbreak in eastern DRC was caused by a distinct Clade I Mpox lineage, differing from historical zoonotic patterns. The outbreak, predominantly affected young adults including a significant proportion of female sex workers, suggests a shift towards human-to-human transmission, potentially involving sexual contact.
Masirika *et al.* [6]	2024	South Kivu	Community	General population	Surveillance and investigation report	Non-probabilistic	Low	Clinical feature	NR	Yes, *n*=2	The findings suggest heterosexual close contact as the main transmission route, highlighting the increased risk for sex workers and their clients in this region.

[1] Date of study completion; VZV: Varicella-Zoster Virus; Surveillance and Investigation Report (Case reports and Case series); NR: Not Reported; DRC: Democratic Republic of Congo; PCR: Polymerase Chain Reaction

Varicella-zoster virus prevalence among suspected Mpox cases

The national pooled prevalence rate of the VZV cases among 64131 suspected Mpox cases was 16.73% (95% CI: 5.36-28.10; n = 8), with I^2 = 99.4% (p < 0.001) (Fig. 2).

The subgroup analysis reveals a notable increase in the suspected Mpox event rate from 1.19% (95% CI: 0.39-2.76; n = 1 study) in 1991-2010 to 19.06% (95% CI: 6.96-31.17; n = 7 studies) in 2011-2024. Substantial heterogeneity (p < 0.001) existed across most subgroups, indicating considerable variation in event rates between studies. Regionally, the highest proportion was observed in the Northeastern region (32.61%; 95% CI: 24.88-41.10; n = 1 study), and among healthcare workers (14.29%; 95% CI: 1.78-42.81; n = 1 study), while setting and participant type also demonstrated varying event rates (Table 2 and Supplementary file 2, Supplementary Fig. 1-5).

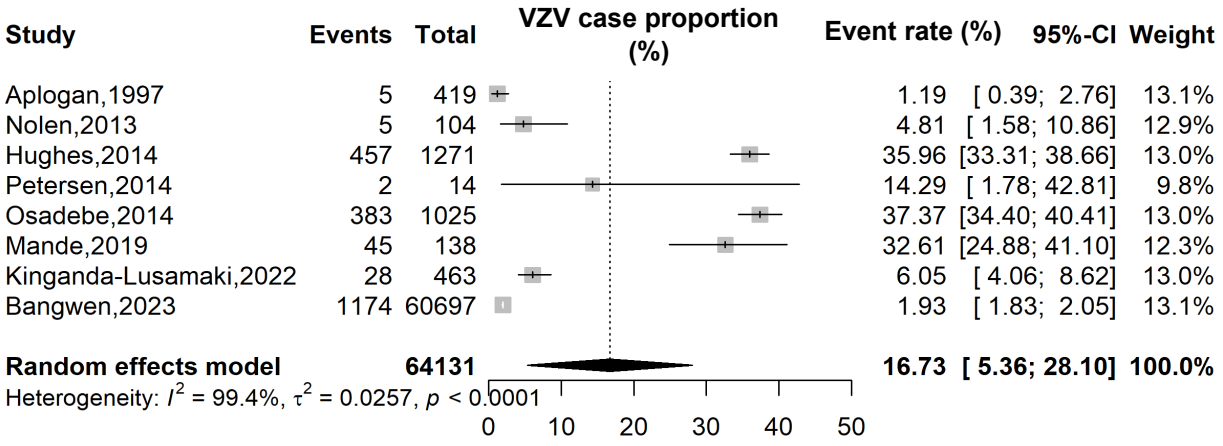

Fig. 2 Pooled estimate of the prevalence rate of varicella-zoster virus isolated among suspected Mpox cases in DRC

Varicella-zoster virus and Mpox coinfection

A total of 1841 confirmed Mpox cases were examined, with the pooled coinfection rate of VZV estimated at 9.69% (95% CI: 1.33-18.06; n = 8 studies) in the country. Significant heterogeneity was observed across these studies (I^2 = 96.9%, p < 0.001) (Fig. 3).

The subgroup analysis of coinfection cases indicates relatively stable event rates across the study periods of 1991-2010 (12.50%; 95% CI: 1.55-38.35; n = 1 study) and 2011-2024 (9.47%; 95% CI: 0.11-18.82; n = 6), although the latter period benefits from more extensive data (n = 7 studies). Significant heterogeneity (p < 0.001) was prevalent across several subgroups, suggesting considerable variability in event rates between studies. Regionally, Equateur reported an event rate of 11.10%; (95% CI : 1.69-20.51; n = 6) while Kivu regions showed

a higher rate (33.33%; 95% CI : 0.84-90.7) based on limited data (n = 1). Similarly, participant type and disease burden categories exhibited varying event rates, often accompanied by substantial heterogeneity (Table 3 and Supplementary file 3, Fig.1-5).

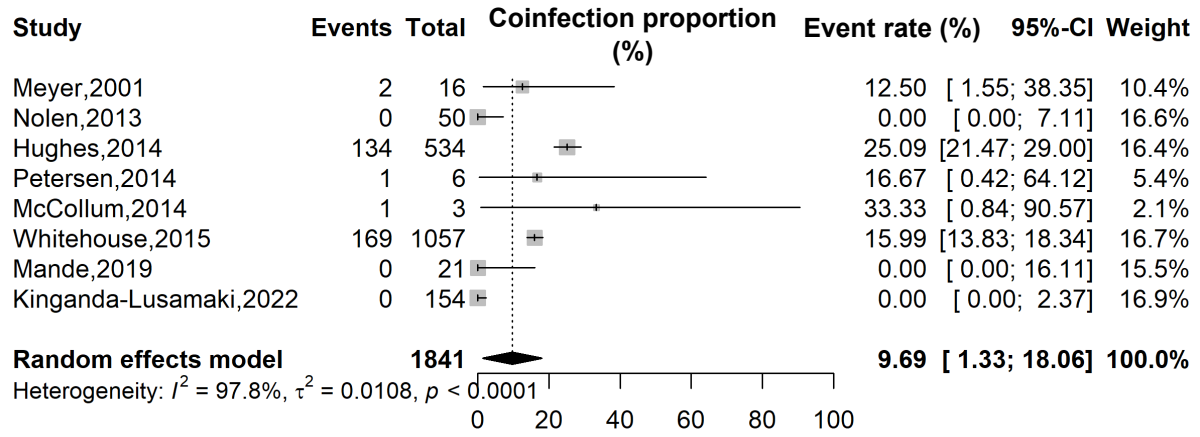

Fig. 3 Pooled estimate of the coinfection proportion of varicella-zoster virus among confirmed Mpox cases in DRC

HIV and Mpox coinfection

The HIV coinfection rate among 1652 confirmed Mpox cases was 0.52% (95% CI: 0.18-0.87) with a low heterogeneity (I^2 = 39.2%, p = 0.160) between studies included (n = 5) (Fig. 4).

The meta-analysis of HIV and Mpox coinfection in the DRC indicates a generally low pooled proportion, with a slight increase observed in 2011-2024 (0.52%; 95% CI: 0.18-0.87; n = 4 studies) compared to earlier (0.00%; 95% CI: 0.00-40.96; n = 1 study). Regional variations showed a higher proportion in South Kivu (1.64%; 95% CI: 0.61-2.66; n = 3 studies). Furthermore, a higher coinfection proportion was found in settings with a lower Mpox burden (3.01%; 95% CI: 0.34-5.68; n = 3 studies) (Table 4, Supplementary file 4, Supplementary Fig. 1-5).

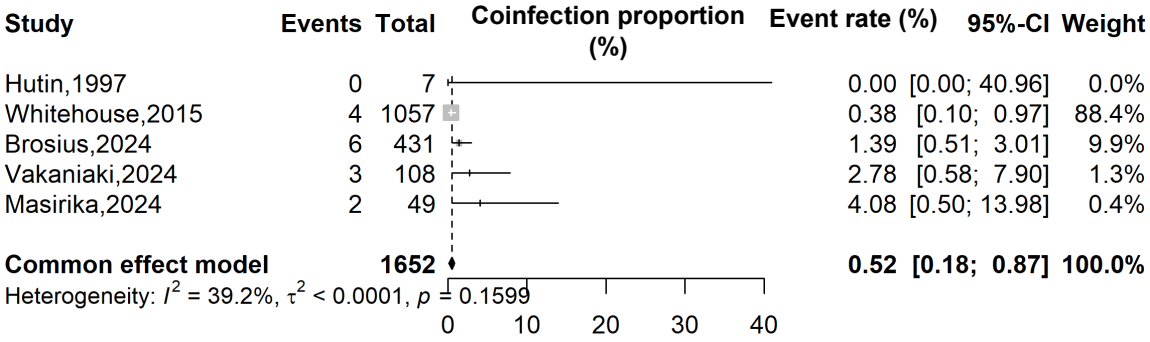

Fig. 4 Pooled estimate of the coinfection proportion of HIV among confirmed Mpox cases in DRC

Subgroup analysis

Table 2 Subgroup meta-analysis of varicella-zoster virus pooled estimate proportion among Mpox suspected case in DRC

Subgroup	Suspected Mpox cases	Event rate[1] (%)	95% CI limits [1]		Number of studies	Heterogeneity statistic[1]	
Study period[2]			**Lower**	**Upper**		I^2 (%)	*p*-value
1991-2010	419	1.19	0.39	2.76	1	-	-
2011-2024	63712	19.06	6.96	31.17	7	99.5	<0.001
Region[3]							
Northeastern	138	32.61	24.88	41.10	1	-	-
Central/Western	2833	18.93	3.31	34.54	5	99.6	<0.001
Nationwide	61160	3.84	0.00	7.86	2	92.7	<0.001
Setting							
Community	3434	18.96	6.75	31.16	7	99.4	<0.001
Online	60697	1.93	1.83	28.10	1	-	-
Participant							
General population	64013	19.05	4.76	33.33	6	99.6	<0.001
General population and HCWs	104	4.81	1.58	10.86	1	-	-
HCWs	14	14.29	1.78	42.81	1	-	-
Disease burden (suspected Mpox cases)							
<400	256	17.25	0.00	34.69	3	94.8	<0.001
≥400	63875	16.46	0.25	32.67	5	99.7	<0.001

[1] Random effects model; CI: Confidence Interval; [2] 1970–1990: Limited healthcare infrastructure in endemic regions; 1991-2010: Improvements in healthcare access and disease surveillance; 2011-2024: Strengthened global health initiatives and response systems; [3] Northeastern=Bas-Uélé, Central/Western= Tshuapa and Kasai oriental; HCW: Healthcare Worker

Table 3 Subgroup meta-analysis of the pooled estimate proportion varicella-zoster virus and Mpox coinfection in DRC

Subgroup	Confirmed Mpox cases	Event rate[1] (%)	95% CI limits[1]		Number of studies	Heterogeneity statistic[1]	
Study period[2]			Lower	Upper		I^2 (%)	*p*-value
1991-2010	16	12.50	1.55	38.35	1	-	-
2011-2024	1825	9.47	0.11	18.82	7	98.1	<0.001
Region[3]							
Equateur	1684	11.10	1.69	20.51	6	96.7	<0.001
Kivu	3	33.33	0.84	90.7	1	-	-
Nationwide	154	0.00	0.00	2.37	1	-	-
Participant							
General population	1785	11.33	1.42	21.24	6	98.4	<0.001
General population and HCWs	50	0	0.00	7.11	1	-	-
HCWs	6	16.67	0.42	64.12	1	-	-
Disease burden (confirmed cases)							
<40	46	2.51	0.00	8.19	4	29.1*	0.237
≥40	1795	10.21	0.00	22.35	4	99.1	<0.001

[1]Random effects model; CI: Confidence interval; [2]1970–1990: Limited healthcare infrastructure in endemic regions; 1991-2010: Improvements in healthcare access and disease surveillance; 2011-2024: Strengthened global health initiatives and response systems; [3] Equateur = Equateur, Tshuapa and Bas-Uélé; Kivu = North and South Kivu; * Fixed effect model applied

Table 4 Subgroup meta-analysis of the pooled estimate proportion of HIV and Mpox coinfection in DRC

Subgroup	Confirmed cases	Event rate[1] (%)	95% CI limits[1]		Number of studies	Heterogeneity statistic[1]	
Study period[2]			Lower	Upper		I^2 (%)	*p*-value
1991-2010	7	0.00	0.00	40.96	1	-	-
2011-2024	1645	0.52	0.18	0.87	4	54.4	0.087
Region[3]							
South Kivu	588	1.64	0.61	2.66	3	0.0	0.483
Other	1064	0.38	0.01	0.75	2	0.0	0.965
Study design							
Cross-sectional	431	1.39	0.51	3.01	1	-	-
Surveillance and Investigation	1221	0.43	0.06	0.79	4	24.1	0.267
Study setting							
Community	1221	0.43	0.06	0.79	4	24.1	0.267
Hospital	431	1.39	0.51	3.01	1	-	-
Disease burden (confirmed cases)							
<110	164	3.01	0.34	5.68	3	0.0	0.866
≥110	1488	0.48	0.13	0.83	2	65.5	0.089

[1] Fixed effects model; CI: Confidence interval; [2]1970–1990: Limited healthcare infrastructure in endemic regions; 1991-2010: Improvements in healthcare access and disease surveillance; 2011-2024: Strengthened global health initiatives and response systems; [3] Equateur: Equateur, Tshuapa and Bas-Uélé; Kivu: North and South Kivu;

Mpox clinical profile

This comprehensive analysis of confirmed Mpox cases in the DRC reveals distinct clinical patterns, with rash being the most universal manifestation (99.97%; 95% CI: 99.85-100.00%), followed by painful lesions (78.17%) and malaise (77.14%). vaginal lesions (60.97%) and oral lesions (44.22%) showed significant incidence, while systemic symptoms like fever (67.94%) and lymphadenopathy (71.99%) were also common. High heterogeneity ($I^2 > 90\%$ for most symptoms, $p < 0.001$) in the data indicates variation between studies. Severe manifestations like convulsions (0.23%), hemorrhagic lesions (2.78%), and hypotension (1.39%) were rare but documented (Table 5, Fig. 5 and Supplementary file 5, Supplementary Fig.1).

An almost similar clinical pattern of Mpox was observed among suspected cases, featuring a near-universal presentation of rash (99.43%, 95% CI: 98.92–99.94) and fever (98.91%, 95% CI: 98.32–99.50). Painful lesions (91.17%) and lymphadenopathy (68.93%) were also prevalent, while systemic symptoms such as fatigue (58.11%) and myalgia (49.49%) occurred moderately. Notably, conjunctivitis (9.92%) and diarrhea (10.91%) were infrequent but non-negligible. Heterogeneity was high for most symptoms ($I^2 > 90\%$, $p < 0.001$). Rare but severe features (e.g., bedridden status: 18.44%) and demographic-specific patterns (e.g., genital lesions: 34.00%) were also described (Supplementary file 6, Supplementary Table 1, Supplementary Fig 1 and 2).

Table 5 Clinical pattern of confirmed Mpox cases in DRC

Rank	Clinical manifestation	Confirmed cases examined (*n*)	Frequency (%)	95% CI Limits		k	Heterogeneity statistic[1]	
				Lower	Upper		I^2 (%)	*p*-value
1	Rash	2987	99.97	99.85	100.00	9	73.2	<0.001
2	Painful lesion	426	78.17	74.25	82.09	1	-	-
3	Malaise	963	77.14	69.10	85.18	3	88.5	<0.001
4	Pruritus or itchy lesion	1764	74.73	52.41	97.05	4	99.1	<0.001
5	Palm lesions	1067	71.54	46.04	97.04	4	99.5	<0.001
6	Lymphadenopathy	2943	71.99	59.27	84.71	9	98.7	<0.001
7	Fatigue or asthenia	1029	70.25	43.92	96.57	5	98.9	<0.001
8	Fever	2936	67.94	43.00	92.88	9	99.9	<0.001
9	Genital lesions	1015	60.97	31.24	90.70	5	99.0	<0.001
10	Chills or sweat	1714	60.95	34.53	87.38	5	97.4	<0.001
11	Sore throat or dysphagia	2923	61.26	47.88	74.65	7	96.8	<0.001
12	Sole lesions	1067	61.17	31.91	90.43	4	99.6	<0.001
13	Headache	2222	57.42	37.66	77.17	7	98.8	<0.001
14	Myalgia	1896	54.07	27.39	80.75	6	99.6	<0.001
15	Anorexia	645	53.86	47.18	60.55	2	63.4	0.098
16	Cough	2928	40.88	29.62	52.15	8	95.7	<0.001
17	Oral lesions	2910	41.22	28.68	53.76	9	97.6	<0.001
18	Dysuria	425	39.53	34.88	44.18	1	-	-
19	Light sensitivity	1322	33.05	30.52	35.59	2	0.0	0.809
20	Anal lesions	645	31.55	27.17	35.94	1	-	-
21	Rhinorrhea	216	31.02	24.85	37.19	1	-	-
22	Abdominal pain	640	26.90	20.02	33.78	2	73.4	0.052
23	Painful eye	426	19.95	16.26	24.07	1	-	-
24	Corneal lesions	303	19.54	0.00	52.54	2	90.1	0.002

25	Bedridden status	2206	18.59	7.56	29.62	5	99.0	<0.001
26	Vomiting or nausea	2264	16.42	7.98	24.83	5	97.3	<0.001
27	Conjunctivitis	2399	14.13	7.64	20.62	7	97.0	<0.001
28	Joint pain	216	13.89	9.28	18.50	1	-	-
29	Back pain	216	11.57	7.31	15.84	1	-	-
30	Rectal pain	424	10.85	7.89	13.81	1	-	-
31	Dyspnea	926	10.47	6.55	14.40	3	75.4	0.017
32	Diarrhea	926	7.71	2.93	12.49	3	86.9	<0.001
33	Ear pain	216	6.94	3.55	10.33	1	-	-
34	Visual Problem	642	6.02	0.00	13.41	2	94.5	<0.001
35	Chest pain	216	5.09	2.16	8.02	1	-	-
36	Hematuria	428	5.14	3.05	7.23	1	-	-
37	Confusion	645	4.10	1.00	7.20	2	68.7	0.074
38	Neck stiffness	216	4.17	1.50	6.83	1	-	-
39	Dehydration	216	3.24	0.88	5.60	1	-	-
40	Hemorrhagic skin lesions	216	2.78	0.59	4.97	1	-	-
41	Petechiae	216	0.93	0.00	2.20	1	-	-
42	Hypothermia	216	1.39	0.00	2.95	1	-	-
43	Convulsions	429	0.23	0.00	0.69	1	-	-
44	Earing problem	216	0.46	0.00	1.37	1	-	-
45	Oedema	216	0.46	0.00	1.37	1	-	-

k=Number of studies; CI: Confidence interval; [1]: Random effect model

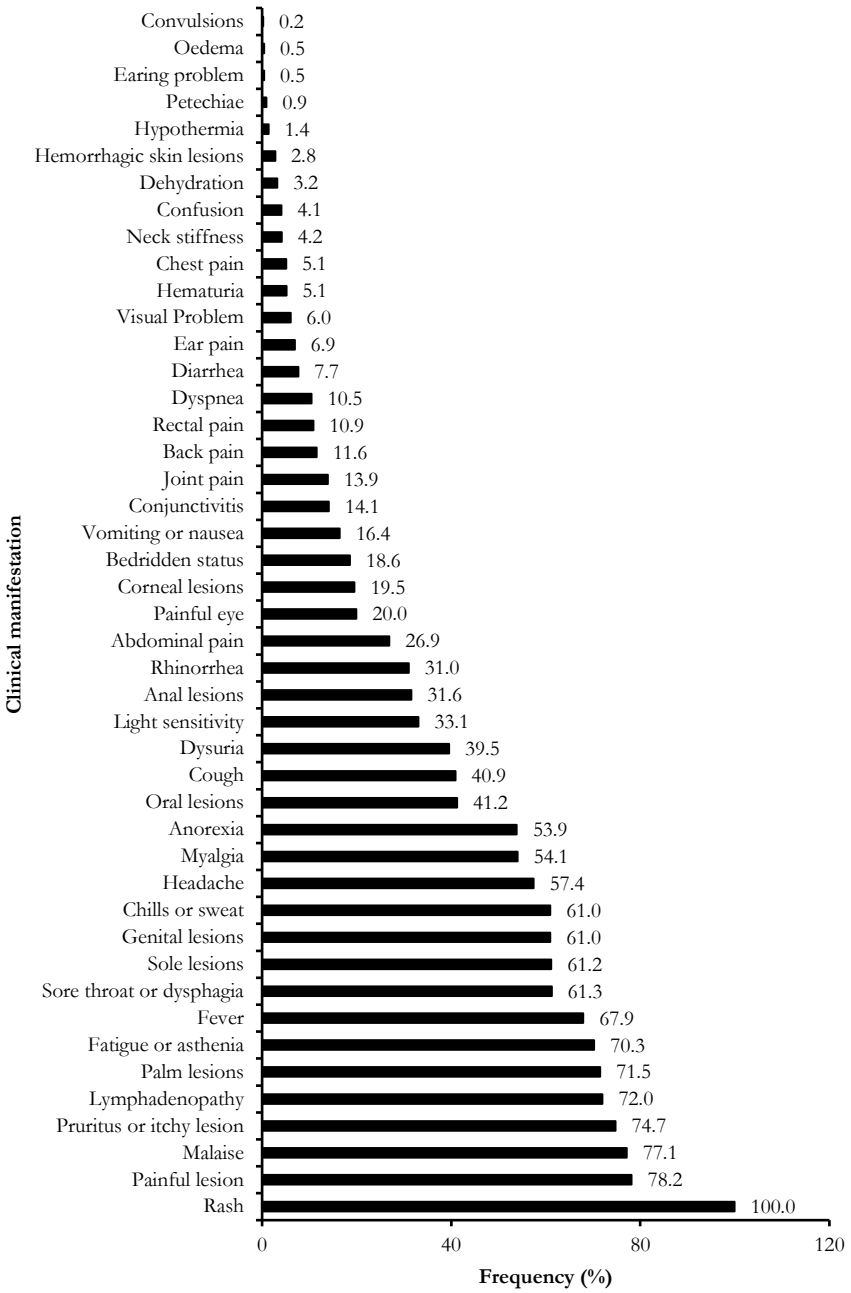

Fig. 5 Trend of clinical manifestations observed among confirmed Mpox cases in DRC,1970-2024

Meta-regression analysis

The multivariate analysis of suspected Mpox cases revealed a significant temporal increase in VZV prevalence ($\beta = 0.2247$, $p < 0.001$), while regional studies exhibited significantly higher VZV estimates compared to nationwide ones ($\beta=4.7148$, $p <0.001$). For confirmed Mpox cases, regional studies had higher VZV estimates ($\beta = 4.2220$, $p = 0.018$). South Kivu had significantly higher HIV co-infection rates among confirmed Mpox

cases compared to other regions (β = 3.608, p = 0.002). Participant type (p = 0.577 and p=0.266), disease burden for suspected cases (p = 0.164), study year for confirmed cases (p = 0.959), study design (p = 0.826), and setting (p = 0.159) did not significantly explain heterogeneity at both uni- and multivariate analysis (Table 6).

Table 6 Meta-regression to explore sources of heterogeneity in the pooled estimate of varicella-zoster virus infection among suspected and confirmed Mpox cases in the DRC, 1970-2024

Epidemiological estimate	Moderator	Univariate		Multivariate	
		Unadjusted coefficient (β)	*p*-value	Adjusted coefficient (β)	*p*-value
VZV among suspected Mpox cases					
Study year	Years	0.0532	0.489	0.2247	<0.001
Region	Regional vs. Nationwide	-1.5582	0.192	4.7148	<0.001
Participant	General population vs. Other	0.2986	0.833	0.5377	0.577
Disease burden[1]	<400 vs. ≥400	0.5960	0.627	-1.2899	0.164
VZV among confirmed Mpox cases					
Study year	Years	-0.1049	0.293	0.0046	0.959
Region	Regional vs. Nationwide	4.1257	0.006	4.2220	0.018
Participant	General population vs. Other	0.8139	0.554	1.2466	0.266
Disease burden	<40 vs. ≥40	0.7141	0.5589	0.0275	0.976
HIV among confirmed Mpox cases					
Study year	Years	-0.0030	0.964	-0.1592	0.063
Region	South Kivu vs. Others	1.3090	0.087	3.608	0.002
Study design[1]	SIR vs. Cross-sectional	0.3004	0.826	-	-
Setting	Hospital vs. Community	-0.3004	0.826	-0.863	0.159
Disease burden[1]	<110 vs. ≥110	1.5627	0.033	-	-

[1] Redundant predictor dropped from the model; VZV: Varicella-zoster virus; HIV: Human immunodeficiency virus; Others included Sankuru and Tshuapa Regions; SIR: Surveillance and investigation report (Case series)

Publication bias

The funnel plot asymmetry suggested a risk of publication bias for our study outcomes. The trim-and-fill analysis suggested four potentially missing studies and not significantly reducing the pooled VZV prevalence among suspected Mpox cases from 16.7% (95% CI: 5.36-28.10) to 2.73% (95% CI: 0.00–18.47). After adjusting for three potentially missing studies, the pooled varicella-zoster virus and Mpox coinfection rate was 4.00% (95% CI: 0.00-13.85), not significantly different from the initial pooled estimate of 9.69% (95% CI: 1.33-18.06). Regarding HIV and Mpox coinfection, two potentially missing studies were suggested by the method, there was no significant difference between the initial rate of 0.52% (95% CI: 0.18-0.87) to 0.70% (95% CI: 0.00-1.60). (Supplementary files 2,3 and 4, Supplementary Fig. 6 and 7).

Sensitivity test analysis

Sensitivity analysis of the pooled prevalence estimate of VZV among suspected Mpox cases demonstrated stable pooled estimates (95% CI: 1.88–2.17%) upon the exclusion of individual studies, supporting the robustness of the primary findings. However, omitting the Bangwen *et al.* study [17] resulted in an outlier effect (8.60%; 95% CI: 7.78–9.43), indicating that this study disproportionately influenced the meta-analysis, possibly due to unique sample characteristics or methodological differences. Sensitivity analysis of the pooled VZV and Mpox coinfection rate also revealed stable estimates (95% CI: 0.47–3.88 events/100 observations) when most studies were excluded. Conversely, excluding the Kinganda-Lusamaki *et al.* study [16] inflated the estimate to 11.66 events/100 observations, highlighting its outlier influence. The exclusion of any study from the meta-analysis had no significant impact on the pooled estimates of the HIV and Mpox coinfection rate (Supplementary file 2; supplementary fig. 8, Supplementary file 3; Supplementary fig. 7, and Supplementary file; Supplementary fig. 8, respectively).

Discussion

Varicella-zoster virus-Mpox coinfection

A pooled VZV coinfection rate of 9.69% was found in our meta-analysis among 1,841 confirmed Mpox cases in the DRC. Significant heterogeneity indicated a high degree of variation among the included studies. Subgroup analyses provided additional information on these differences. Despite increased surveillance efforts in the latter era, coinfection rates demonstrated temporal stability, with comparable rates recorded in 1991–2010 and 2011–2024. Regional differences were also observed; the Equateur region had a coinfection rate of 11.10% (across six studies), while the Kivu region had a higher rate of 33.33% (based on a single study).

The clinical similarities between VZV and Mpox rashes may lead to diagnostic overlap and misclassification, particularly in settings where PCR confirmation is limited [43]. The temporal stability of coinfection rates, despite improved diagnostics after 2010, suggests the influence of persistent underlying ecological drivers, such as deforestation and human encroachment [3].

Our findings were lower than those obtained from studies conducted in Nigeria, which reported that 27-81% of confirmed Mpox cases were coinfected with VZV [28,44]. Meanwhile, a study conducted in Belgium reported no cases of VZV among confirmed Mpox cases, suggesting that VZV did not cocirculate in the population at risk for Mpox during the Belgian 2022 outbreak, and also that Mpox does not commonly trigger reactivation of latent VZV in adult men [45].

The VZV coinfection might have been responsible for more severity and complications among confirmed Mpox cases in DRC, as described in a study conducted in Nigeria (coinfected patients had more

complications than Mpox-only infected cases (56.3% vs. 22.5%, p = 0.015) [44]. In addition, in some epidemiological contexts, rodents infected with the poxvirus could transmit the disease through VZV skin lesions and cause coinfection. Based on that hypothesis, the authors concluded that varicella infection is a risk factor for the acquisition of Mpox [46].

These findings have important implications for clinical practice and public health strategies in the DRC. In order to reliably distinguish between VZV and Mpox coinfections and single infections, they emphasize the necessity of dual diagnostic techniques that may include PCR and serological testing [12]. Furthermore, because their clinical profile may more severity, coinfected patients may need additional care while in the hospital [44].

HIV-Mpox coinfection

Among 1652 confirmed Mpox cases, the HIV coinfection rate was 0.52% with low heterogeneity between the five included studies. On the other hand, within a gender-specific group from industrialized nations, a study found a much greater percentage of HIV coinfection among confirmed Mpox cases (35%)[21]. According to a meta-analysis, those who had both HIV and Mpox were more likely to be hospitalized than people who just had Mpox (OR = 1.85; 95% CI 0.918–3.719; p = 0.085). This provides evidence that HIV and Mpox coinfection has a negative impact on clinical outcomes, including patient death [18]. Similar conclusions were drawn in a report from Nigeria [19].

Mpox clinical pattern

Rash, painful lesions, and malaise were the main clinical presentation, indicating that these symptoms should be included in Mpox case criteria. The high heterogeneity among studies highlights significant inconsistency in clinical reporting [1].

The WHO and CDC case definitions, which emphasize rash as a cardinal symptom for probable Mpox, are consistent with the nearly universal prevalence of rash [1,9]. The high prevalence of painful lesions is a crucial diagnostic marker for differentiating Mpox in endemic places, even though it was only observed in one study. This result validates the DRC guidelines' inclusion of painful rash in clinical algorithms [1].

Differential diagnosis is made more difficult by the predominance of systemic symptoms (fever, lymphadenopathy), which overlap with malaria, VZV, and other febrile disorders that are endemic to the DRC [47,48]. However, afebrile rash presentations should not be excluded from Mpox due to the reduced fever prevalence relative to rash, which challenges previous definitions that required fever as a necessary requirement [49].

This study highlights the need to expand clinical criteria to capture atypical presentations [50]. Given the overlapping symptoms with other endemic diseases, the high heterogeneity ($I^2 > 90\%$) in symptom reporting

highlights the significance of standardizing clinical assessments and implementing dual-pathogen testing (Mpox/VZV PCR) to improve diagnostic accuracy [10].

Strength and limitations

This review has several limitations. The small number of included studies (<10) constrained us to rely only on the funnel plot to assess publication bias, as the traditional Egger and Begg's tests could not be performed. Furthermore, the precision of the results was limited by the large confidence intervals produced by the small sample sizes in some subgroup analyses. The strength of this systematic review and meta-analysis relies on the fact that it provides insightful information about Mpox coinfection with other viral illnesses in the DRC, such as VZV and HIV. The results emphasize the necessity of public health surveillance, and actions to lessen and avoid disease complication among infected patients.

Conclusions

The clinical profile of Mpox in the DRC is marked by almost universal rash manifestation and frequent systemic symptoms (Malaise, painful lesions). This study also identifies inadequacies in the current case definitions and surveillance methods. There is a need for standardized, context-adapted diagnostic methods that incorporate dual-pathogen testing and broaden criteria to identify atypical presentations. This is highlighted by the considerable variability in symptom reporting and significant VZV coinfection rates. In order to improve early detection and epidemic response in Africa's highest-burden settings, where Mpox continues to pose a significant public health concern, these findings advocate for more investments in laboratory capacity, healthcare worker training, and regionally specific monitoring systems.

Abbreviations

CI: Confidence interval

DRC: Democratic Republic of Congo

HCW: Healthcare worker

HIV: Human immunodeficiency virus

MeSH: Medical subject headings

Mpox: Monkeypox

PCR: Polymerase Chain Reaction

PRISMA: Preferred reporting items for systematic reviews and meta-analysis

VZV: Varicella-zoster Virus

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Standards of Reporting

This systematic review was conducted and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

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Supplementary Material

Supplementary material associated with this article has been published online and is available at: Link to the DOI

References

1. Mpox WHO, Geneva. 2024. Available online: https://www.who.int/news-room/fact-sheets/detail/mpox. Accessed: 2025 Apr 27.

2. Djuicy DD, Sadeuh-Mba SA, Bilounga CN, Yonga MG, Tchatchueng-Mbougua JB, Essima GD, et al. Concurrent Clade I and Clade II Monkeypox Virus Circulation, Cameroon, 1979–2022. *Emerg Infect Dis.* **2024**;30(3):433–43.

3. Cheuyem FZL, Zemsi A, Ndungo JH, Achangwa C, Takpando-le-grand DR, Goupeyou-Youmsi JM, et al. Mpox Severity and Mortality in the Most Endemic Focus in Africa: A Systematic Review and Meta-Analysis (1970-2024). *medRxiv*; **2025**; doi: 10.1101/2025.04.07.25325410v1.

4. Osadebe L, Hughes CM, Shongo Lushima R, Kabamba J, Nguete B, Malekani J, et al. Enhancing case definitions for surveillance of human monkeypox in the Democratic Republic of Congo. Kasper M, editor. *PLoS Negl Trop Dis*. **2017**;11(9): e0005857.

5. Brosius I, Vakaniaki EH, Mukari G, Munganga P, Tshomba JC, Vos ED, et al. Epidemiological and clinical features of mpox during the clade Ib outbreak in South Kivu, Democratic Republic of the Congo: a prospective cohort study. *The Lancet*. **2025**;405(10478):547–59.

6. Masirika LM, Udahemuka JC, Ndishimye P, Martinez GS, Kelvin P, Nadine MB, et al. Epidemiology, clinical characteristics, and transmission patterns of a novel Mpox (Monkeypox) outbreak in eastern Democratic Republic of the Congo (DRC): an observational, cross-sectional cohort study. *medRxiv*; **2024**. doi: 10.1101/2024.03.05.24303395v1

7. Kombozi YDMerci, Singa Valentin. B, Ley. BL, Antoine. ET, Guild. AK, Lwanga. K, et al. MPOX: epidemiological profile and factors associated with its emergence in the Isangi territory, Democratic Republic of Congo. *Int J Appl Sci Eng Rev*. **2024**;5(5):27–43.

8. WHO | The World Health Organisation. WHO Coronavirus (COVID-19) Dashboard.. Available online: https://covid19.who.int. Accessed: 2022 Oct 20.

9. CDC. Signs and Symptoms of Mpox. CDC, Atlanta. **2024**. Available online : https://www.cdc.gov/mpox/signs-symptoms/index.html. Accessed : 2025 Apr 27.

10. Whitehouse ER, Bonwitt J, Hughes CM, Lushima RS, Likafi T, Nguete B, et al. Clinical and Epidemiological Findings from Enhanced Monkeypox Surveillance in Tshuapa Province, Democratic Republic of the Congo During 2011–2015. *J Infect Dis*. **2021**;223(11):1870–8.

11. Hughes CM, Liu L, Davidson WB, Radford KW, Wilkins K, Monroe B, et al. A Tale of Two Viruses: Coinfections of Monkeypox and Varicella Zoster Virus in the Democratic Republic of Congo. *Am J Trop Med Hyg*. **2021**;104(2):604–11.

12. Pittman PR, Martin JW, Kingebeni PM, Tamfum JJM, Mwema G, Wan Q, et al. Clinical characterization and placental pathology of mpox infection in hospitalized patients in the Democratic Republic of the Congo. Bowman N, editor. *PLoS Negl Trop Dis*. **2023**;17(4): e0010384.

13. Kibungu EM, Vakaniaki EH, Kinganda-Lusamaki E, Kalonji-Mukendi T, Pukuta E, Hoff NA, et al. Clade I–Associated Mpox Cases Associated with Sexual Contact, the Democratic Republic of the Congo. *Emerg Infect Dis*. **2024**;30(1):172–6.

14. Mukadi-Bamuleka D, Kinganda-Lusamaki E, Mulopo-Mukanya N, Amuri-Aziza A, O'Toole Á, Modadra-Madakpa B, et al. First imported Cases of MPXV Clade Ib in Goma, Democratic Republic of the Congo: Implications for Global Surveillance and Transmission Dynamics. *medRxiv*; **2024**; doi: 10.1101/2024.09.12.24313188.

15. Mpox - Democratic Republic of the Congo. WHO, Geneva. **2024**. Available online: https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON522. Accessed: 2025 Apr 27.

16. Kinganda-Lusamaki E, Baketana LK, Ndomba-Mukanya E, Bouillin J, Thaurignac G, Aziza AA, et al. Use of Mpox Multiplex Serology in the Identification of Cases and Outbreak Investigations in the Democratic Republic of the Congo (DRC). *Pathogens*. **2023**;12(7):916.

17. Bangwen E, Diavita R, Vos ED, Vakaniaki EH, Nundu SS, Mutombo A, et al. Suspected and confirmed mpox cases in DR Congo: a retrospective analysis of national epidemiological and laboratory surveillance data, 2010–23. *The Lancet*. **2025**;405(10476):408–19.

18. Taha AM, Elrosasy A, Mahmoud AM, Saed SAA, Moawad WAE, Hamouda E, et al. The effect of HIV and mpox co-infection on clinical outcomes: Systematic review and meta-analysis. *HIV Med*. **2024**;25(8):897–909.

19. Mmerem JI, Johnson SM, Iroezindu MO. Monkeypox and chickenpox co-infection in a person living with Human Immunodeficiency Virus. *J Infect Dev Ctries*. **2024**;18(07):1152–6.

20. Tati G. Territory and border crossing for livelihoods among (voluntary and forced) migrants from DRC to Swaziland: the re-imagining of a borderless spatial system. In: Udelsmann Rodrigues C, Tomàs J, editors. Crossing African Borders: Migration and Mobility. *Lisboa: Centro de Estudos Internacionais*; **2012**. p. 126–44. (ebook'IS).

21. Liu BM, Rakhmanina NY, Yang Z, Bukrinsky MI. Mpox (Monkeypox) Virus and Its Co-Infection with HIV, Sexually Transmitted Infections, or Bacterial Superinfections: Double Whammy or a New Prime Culprit? *Viruses*. **2024**;16(5):784.

22. Doshi RH, Guagliardo SAJ, Dzabatou-Babeaux A, Likouayoulou C, Ndakala N, Moses C, et al. Strengthening of Surveillance during Monkeypox Outbreak, Republic of the Congo, 2017. *Emerg Infect Dis*. **2018** ;24(6):1158–60.

23. Musuka G, Moyo E, Tungwarara N, Mhango M, Pierre G, Saramba E, et al. A critical review of mpox outbreaks, risk factors, and prevention efforts in Africa: lessons learned and evolving practices. *IJID Reg*. **2024**;12(2024):100402.

24. Martins-Filho PR, Dorea FCM, Sena LOC, Bezerra GVB, Teixeira DCP, Damaso CR, et al. First reports of monkeypox and varicella-zoster virus coinfection in the global human monkeypox outbreak in 2022. *Travel Med Infect Dis*. **2023**; 51:102510.

25. Du M, Niu B, Liu J. The research and development landscape for mpox vaccines. *Lancet Infect Dis. 2025*;25(4): e198-9.

26. Shafaati M, Forghani S, Shahsavand Davoudi A, Samiee R, Mohammadi K, Akbarpour S, et al. Current advances and challenges in mpox vaccine development: a global landscape. *Ther Adv Vaccines Immunother*. **2025**; 13:25151355251314339.

27. Petrichko S, Kindrachuk J, Nkamba D, Halbrook M, Merritt S, Kalengi H, et al. Mpox Vaccine Acceptance, Democratic Republic of the Congo. *Emerg Infect Dis*. **2024**;30(12):2614–9.

28. Stephen R, Alele F, Olumoh J, Tyndall J, Okeke MI, Adegboye O. The epidemiological trend of monkeypox and monkeypox-varicella zoster viruses' co-infection in North-Eastern Nigeria. *Front Public Health*. **2022** ;10. doi: 10.3389/fpubh.2022.1066589.

29. Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Med.* **2009**;6(7):e1000097.

30. Hutin YJF, Williams RJ, Malfait P, Pebody R, Loparev VN, Ropp SL, et al. Outbreak of Human Monkeypox, Democratic Republic of Congo, 1996 to 1997. *Emerg Infect Dis.* **2001**;7(3):434–8.

31. JBI Critical Appraisal Tools. The Joanna Briggs Institute, Adelaide. **2017**. Available from: https://jbi.global/critical-appraisal-tools. Accessed2024 Dec 3.

32. R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. 2024. Available from: https://www.R-project.org/. Accessed 2024 Dec 19.

33. Shi L, Lin L. The trim-and-fill method for publication bias: practical guidelines and recommendations based on a large database of meta-analyses. *Medicine (Baltimore).* **2019**;98(23): e15987.

34. Jezek Z, Szczeniowski M, Paluku KM, Mutombo M. Human Monkeypox: Clinical Features of 282 Patients. *J Infect Dis.* **1987**;156(2):293–8.

35. Aplogan A, Mangindula V, Muamba P, Mwema G, Okito L, Pebody R, et al. Human monkeypox -- Kasai Oriental, Democratic Republic of Congo, February 1996-October 1997. *MMWR Morb Mortal Wkly Rep***. 1997**;46(49):1168–71.

36. Meyer H, Perrichot M, Stemmler M, Emmerich P, Schmitz H, Varaine F, et al. Outbreaks of Disease Suspected of Being Due to Human Monkeypox Virus Infection in the Democratic Republic of Congo in 2001. *J Clin Microbiol.* **2002**;40(8):2919–21.

37. Nolen LD, Osadebe L, Katomba J, Likofata J, Mukadi D, Monroe B, et al. Extended Human-to-Human Transmission during a Monkeypox Outbreak in the Democratic Republic of the Congo. *Emerg Infect Dis.* **2016**;22(6):1014–21.

38. Petersen BW, Kabamba J, McCollum AM, Lushima RS, Wemakoy EO, Muyembe Tamfum JJ, et al. Vaccinating against monkeypox in the Democratic Republic of the Congo. *Antiviral Res.* **2019**; 162:171–7.

39. McCollum AM, Nakazawa Y, Ndongala GM, Pukuta E, Karhemere S, Lushima RS, et al. Human Monkeypox in the Kivus, a Conflict Region of the Democratic Republic of the Congo. *Am Soc Trop Med Hyg.* **2015**;93(4):718–1.

40. Mande G, Akonda I, Weggheleire AD, Brosius I, Liesenborghs L, Bottieau E, et al. Enhanced surveillance of monkeypox in Bas-Uélé, Democratic Republic of Congo: the limitations of symptom-based case definitions. *Int J Infect Dis.* **2022**;122:647–55.

41. Ngbolua K te N, Guy Kumbali Ngambika, Blaise Mbembo-wa-Mbembo, Kohowe Pagerezo Séraphin, Kogana Kapalata Fabrice, Gédéon Ngiala Bongo, et al. First Report on Three Cases of Monkey pox in Nord Ubangi Province (Democratic Republic of the Congo). *Br Int Exact Sci BIoEx J.* **2020**;2(1):120–5.

42. Vakaniaki EH, Kacita C, Kinganda-Lusamaki E, O'Toole Á, Wawina-Bokalanga T, Mukadi-Bamuleka D, et al. Sustained human outbreak of a new MPXV clade I lineage in eastern Democratic Republic of the Congo. *Nat Med.* **2024**;30(10):2791–5.

43. Bourner J, Garcia-Gallo E, Mbrenga F, Boum Y, Nakouné E, Paterson A, et al. Challenges in clinical diagnosis of Clade I Mpox: Highlighting the need for enhanced diagnostic approaches. *PLoS Negl Trop Dis*. **2024**;18(6):e0012087.

44. Mmerem JI, Umenzekwe CC, Johnson SM, Onukak AE, Chika-Igwenyi NM, Chukwu SK, et al. Mpox and Chickenpox Coinfection: Case Series from Southern Nigeria. *J Infect Dis*. **2024**;229(Supplement_2):S260-4.

45. Coppens J, Liesenborghs L, Vercauteren K, Van Esbroeck M, Van Dijck C. No Varicella Zoster Virus Infection among Mpox Cases in Antwerp, Belgium. *Am J Trop Med Hyg*. **2023**;109(6):1282–3.

46. Grose C. Surveillance of Nigerian children suggests that varicella may be a risk factor for acquisition of monkeypox. *Front Public Health*. **2023**; 11:1140956.

47. Endy TP. Viral Febrile Illnesses and Emerging Pathogens. In: Hunter's Tropical Medicine and Emerging Infectious Diseases. *Elsevier*; **2020**. p. 325–50

48. Acute respiratory infections complicated by malaria (previously undiagnosed disease) - Democratic Republic of the Congo. WHO, Geneva. 2024. https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON547. Accessed 2025 Apr 27.

49. Breman JG, Kalisa-Ruti, Steniowski MV, Zanotto E, Gromyko AI, Arita I. Human monkeypox, 1970-79. *Bull World Health Organ*. **1980**;58(2):165–82.

50. Mpox Virus Infection 2022 Case Definition. 2024. https://ndc.services.cdc.gov/case-definitions/monkeypox-virus-infection-2023/. Accessed 2025 Apr 28.