Evidence Synthesis in Healthcare Connect
ISSN: 3105-0123
2026, Article ID. 2026.0002, Cite as: https://doi.org/10.69709/ESHC.2026.183845

SCIFINITI PUBLISHING

Systematic Review

OPEN ACCESS

Mpox and Varicella-Zoster Virus Coinfection in the Democratic Republic of Congo: A Systematic Review and Meta-Analysis

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Article History
Received: November 01, 2025 Accepted: February 20, 2026 Published: March 18, 2026

Abstract

Introduction: Monkeypox (Mpox) is an endemic disease in the Democratic Republic of Congo (DRC). Despite five decades of outbreaks, gaps persist in understanding the clinical patterns of Mpox and its 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 the clinical presentation of Mpox and coinfection trends in the Democratic Republic of the Congo. Estimating the burden of VZV and HIV coinfections can provide valuable insights to inform decision-making in efforts to control this outbreak. **Methods**: Data for this study were systematically extracted from online databases, including PubMed, ScienceDirect, and Google Scholar. The pooled estimates of VZV and HIV coinfection rates was calculated using fixed and random-effects models. Subgroup analyses were carried out based on time period, geographic region, study design, setting, and participant characteristics. **Results:** Among a total of 1841 confirmed Mpox cases, VZV coinfection was 9.69% (95% CI: 1.33–18.06; 8 studies), 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; 8 studies), with $I^2 = 99.4\%$ ($p < 0.001$). The pooled estimate of HIV coinfection at the national level was low (0.52%, 95% CI: 0.18–0.87; 5 studies; n = 1,652) but was higher in South Kivu (1.64%). Among confirmed cases, the most common clinical presentations were rash (99.97%), painful lesions (78.17%), and malaise (77.14%), underscoring their diagnostic significance in case definitions. A similar clinical pattern of Mpox was observed among suspected cases, with nearly all reported cases presenting with 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 Democratic Republic of the Congo presents with an almost universal rash, highlighting its central role in case definitions. These findings provide critical evidence to support enhanced frontline detection and targeted outbreak response in endemic regions.

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

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2026, Vol. 1, Article ID. 2026.0002
https://doi.org/10.69709/ESHC.2026.183845

1. Introduction

The Simian Orthopoxvirus, responsible for monkeypox (Mpox), represents a significant public health threat, especially in areas of Central and West Africa where the disease is endemic [1,2]. The Democratic Republic of Congo (DRC) continues to serve as the epicenter of human Mpox, where the disease has accounted for 4.18% mortality (95% CI: 0.29–8.08) among confirmed cases since its emergence in 1970 [3]. The Mpox virus belongs to the genus Orthopoxvirus, the same genus as the smallpox (variola) virus. Scientists have identified two primary clades of the Mpox virus: Clade I (formerly the Congo Basin clade) and Clade II (formerly 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 2022–2023 global spread of Clade IIb, primarily through sexual contact, demonstrated the virus's potential 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, which progresses through macular, papular, vesicular, and pustular stages before crusting [8,9]. Nonetheless, notable differences have been documented in clinical presentations between several outbreaks and demographic settings [4,10–14]. Accurate clinical diagnosis is challenged by this variability, particularly in resource-limited settings where confirmatory testing may not be available [15]. The situation is further complicated by the co-circulation of varicella-zoster virus (VZV), as Mpox cases may be misdiagnosed or underreported due to the similar cutaneous presentations caused by VZV [10,16,17]. Up to 40% of suspected Mpox cases in the DRC may actually be VZV infections, according to study reports, highlighting the urgent need to strengthen diagnostic capacity in endemic regions [4].

The epidemiological context has become more complex due to human immunodeficiency virus (HIV) as a comorbidity among some Mpox patients [18,19]. Commercial sex work along transit routes, frequent cross-border migration, and extensive social and transport networks all contribute to the regional spread of infectious diseases such as 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 the impact of HIV on the immune response in individuals infected with Clade I Mpox remains unclear, coinfection is likely to exacerbate disease severity, potentially leading to fatal outcomes in the absence of appropriate 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].

Although Mpox has been endemic in the Democratic Republic of the Congo (DRC) for over 50 years, substantial gaps remain in our understanding of its 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, recent advances in molecular diagnostics, such as multiplex polymerase chain reaction (PCR) assays, provide new tools to enhance case detection and can differentiate Mpox from varicella-zoster virus (VZV) [10]. Nonetheless, in the majority of the country, access to these advanced diagnostic instruments is still limited [22]. These difficulties may lead to a delayed diagnosis, insufficient treatment, and a higher Mpox death rate [23]. Furthermore, the 2022 global outbreak underscores the potential for Mpox virus adaptation to sustained human-to-human transmission, highlighting the need for enhanced surveillance in endemic regions to detect changes in clinical presentation or transmission patterns [24].

It is essential to generate updated data on the clinical and paraclinical presentation of Mpox to inform the development of context-specific case definitions for the DRC. This information will also provide evidence to guide clinical management and public health interventions in this high-burden setting. The study is particularly timely given the recent increase in 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 synthesize data on Mpox clinical presentation and coinfection trends in the Democratic Republic of the Congo from 1970 to 2024. The study aimed to estimate the burden of VZV and HIV coinfections by analyzing data from confirmed Mpox cases.

2. Methods

2.1. Study Design

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

2.2. 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].

2.3. 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, duplicate publications were removed, and studies with ambiguous result definitions were excluded. There were no publication date limits, but only original research articles written in English and French were included.

2.4. Article Searching Strategy

PubMed, ScienceDirect, and Google Scholar were systematically searched to identify eligible published studies. 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 S1 and Supplementary Table S1). Additionally, a manual search was conducted to identify publications not indexed in the selected databases. The final search was completed on February 27, 2025.

2.5. Data Extraction

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

2.6. Data Quality Assessment

The quality of the included studies was assessed using the Joanna Briggs Institute (JBI) quality assessment tool [31]. The risk of bias was evaluated 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 ($\geq$60%). (2) For case series, criteria included: standardized measurement and valid identification of the condition for all participants, consecutive and complete inclusion of participants, reporting of participant demographics and clinical information, reporting of outcomes or follow-up results, reporting of the presenting site(s)/clinic(s) demographic information, and statistical analysis appropriate for case series studies. Each criterion was scored as 1 (yes) or 0 (no or unclear). The overall risk of bias was categorized as low (>50%), moderate (>25–50%), or high ($\leq$25%).

2.7. 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–Mpox coinfection rate was calculated by dividing the number of confirmed HIV and Mpox coinfected cases by the total 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 both suspected and confirmed Mpox cases, the proportion of each clinical manifestation was determined by dividing the frequency of the manifestation by the total number of suspected or confirmed cases, respectively.

2.8. Statistical Analysis and Synthesis

The heterogeneity between studies was evaluated using the I^2 statistic, which classified it as low (<25%), mod-

erate (25–75%), or high (>75%). A random-effects model was employed for analyses exhibiting heterogeneity greater than 50%. Subgroup analyses were performed according to study period, geographic region, setting, participant characteristics, 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].

2.9. 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 assess the robustness of the findings, sensitivity analyses were performed by iteratively excluding one study at a time and pooling the resulting estimates.

3. Results

3.1. Studies Selection

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 duplicate records were removed, and 152 unique records underwent title and abstract screening prior to eligibility assessment. Ultimately, 20 study reports met the inclusion criteria and were included in the meta-analysis (Figure 1).

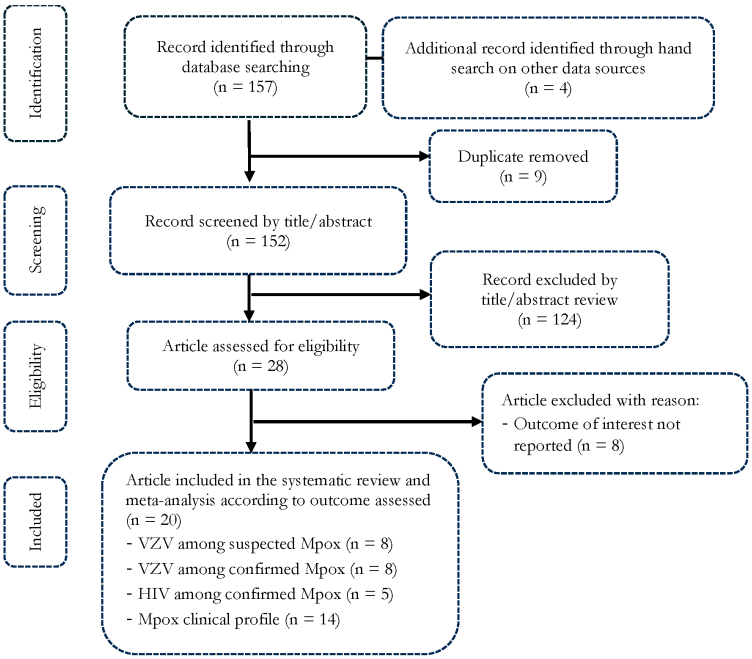

Figure 1: PRISMA diagram flow of studies included in the meta-analysis. (VZV: Varicella-zoster virus; HIV: Human immunodeficiency virus).

3.2. Characteristics of Studies Included

Twenty studies, conducted between 1985 and 2024 in both 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):

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https://doi.org/10.69709/ESHC.2026.183845

Table 1: Characteristics 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 Cases	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 was characterized by 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, and secondary transmission was facilitated by travel and close contact within households and neighborhoods.

Table 1: *Cont.*

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 Cases	Summary of Findings
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 workers	Surveillance and investigation report	Non-probabilistic	Low	VZV coinfection	Yes, $n = 0$	NR	Half of the 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.

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Table 1: *Cont.*

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 Cases	Summary of Findings
Hughes et al. [11]	2014	Tshuapa	Community	General population	Surveillance and investigation report	Non-probabilistic	Low	VZV coinfection and Clinical features	Yes, *n* = 134	NR	A significant proportion of Mpox cases were co-infected with VZV, with atypical clinical presentations that highlight 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 features	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.

Table 1: *Cont.*

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 Cases	Summary of Findings
Whitehouse et al. [10]	2014	Tshuapa	Community	General population	Surveillance and investigation report	Non-probabilistic	Low	VZV coinfection and Clinical features	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 features	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 cases 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 features	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 in 14 additional health zones and proving current surveillance misses over 40% of cases.

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Table 1: *Cont.*

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 Cases	Summary of Findings
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 fourfold increase in incidence between 2010 and 2023, a wider geographic spread, and a 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 et 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.

Table 1: *Cont.*

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 Cases	Summary of Findings
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 that differed from historical zoonotic patterns. The outbreak, predominantly affecting young adults, including a significant proportion of female sex workers, suggests a shift towards human-to-human transmission, potentially involving sexual contact. The findings suggest heterosexual close contact as the main transmission route, highlighting the increased risk for sex workers and their clients in this region.
Masirika et al. [6]	2024	South Kivu	Community	General population	Surveillance and investigation report	Non-probabilistic	Low	Clinical feature	NR	Yes, $n = 2$	

[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.

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3.3. Varicella-Zoster Virus Prevalence Among Suspected Mpox Cases

The national pooled prevalence rate of VZV among 64,131 suspected Mpox caseswas 16.73% (95% CI: 5.36–28.10; n = 8), with I^2 = 99.4% (p < 0.001) (Figure 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) was observed 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 S2, Supplementary Figures S1–S5).

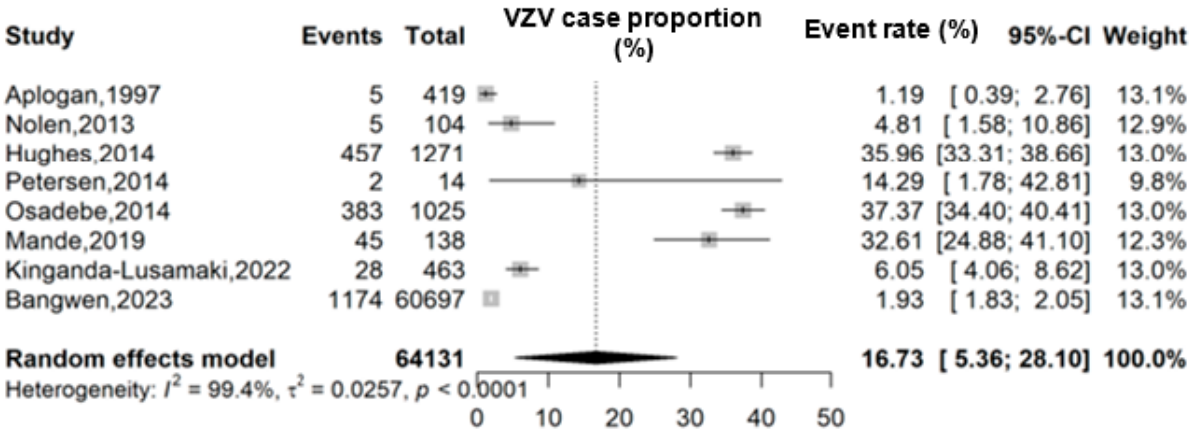

Figure 2: Pooled estimate of the prevalence rate of varicella-zoster virus isolated among suspected Mpox cases in DRC.

Table 2: Subgroup meta-analysis of the pooled estimate of varicella-zoster virus proportion among suspected Mpox cases 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	63,712	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	61,160	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	60,697	1.93	1.83	28.10	1	-	-
Participant							
General population	64,013	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	63,875	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.

3.4. Varicella-Zoster Virus and Mpox Coinfection

A total of 1841 confirmed Mpox cases were analyzed, and the pooled coinfection rate of VZV was 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) (Figure 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 = 7 studies), 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, event rates varied across participant types and disease burden categories, often showing substantial heterogeneity (Table 3; Supplementary File S3, Figures S1–S5).

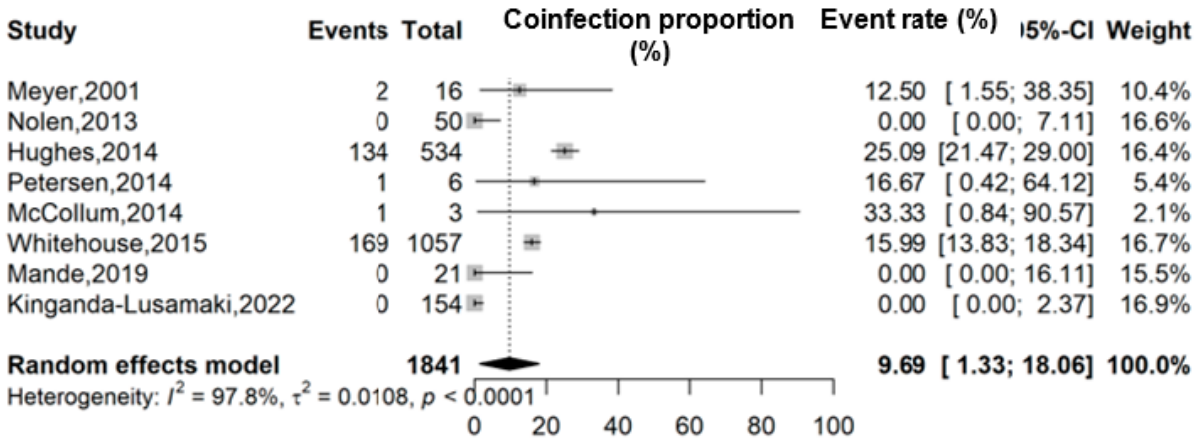

Figure 3: Pooled estimate of the coinfection proportion of varicella-zoster virus among confirmed Mpox cases in DRC.

Table 3: Subgroup meta-analysis of the pooled estimate of 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.

3.5. 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) (Figure 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 S4, Supplementary Figures S1–S5).

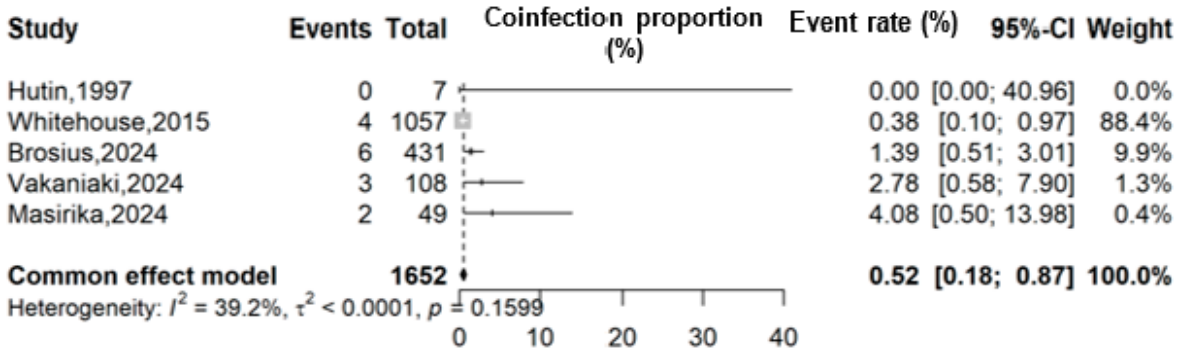

Figure 4: Pooled estimate of the coinfection proportion of HIV among confirmed Mpox cases in DRC.

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.

3.6. 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%). Genital lesions (60.97%) and oral lesions (41.22%) were observed with notable frequency, while systemic symptoms such as fever (67.94%) and lymphadenopathy (71.99%) were also commonly reported. 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 hypothermia (1.39%) were rare but documented (Table 5, Figure 5, and Supplementary File S5, Supplementary Figure S1).

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	Hearing	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.

A similar clinical pattern was observed among suspected Mpox cases, with nearly 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%) were moderately prevalent. Notably, conjunctivitis (9.92%) and diarrhea (10.91%) were infrequent

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https://doi.org/10.69709/ESHC.2026.183845

but non-negligible. Heterogeneity was high for most symptoms ($I^2 > 90\%$, $p < 0.001$). Rare but severe clinical features, such as bedridden status (18.44%), and demographic-specific patterns, including genital lesions (34.00%), were also reported (Supplementary File S6, Supplementary Table S1, Supplementary Figures S1 and S2).

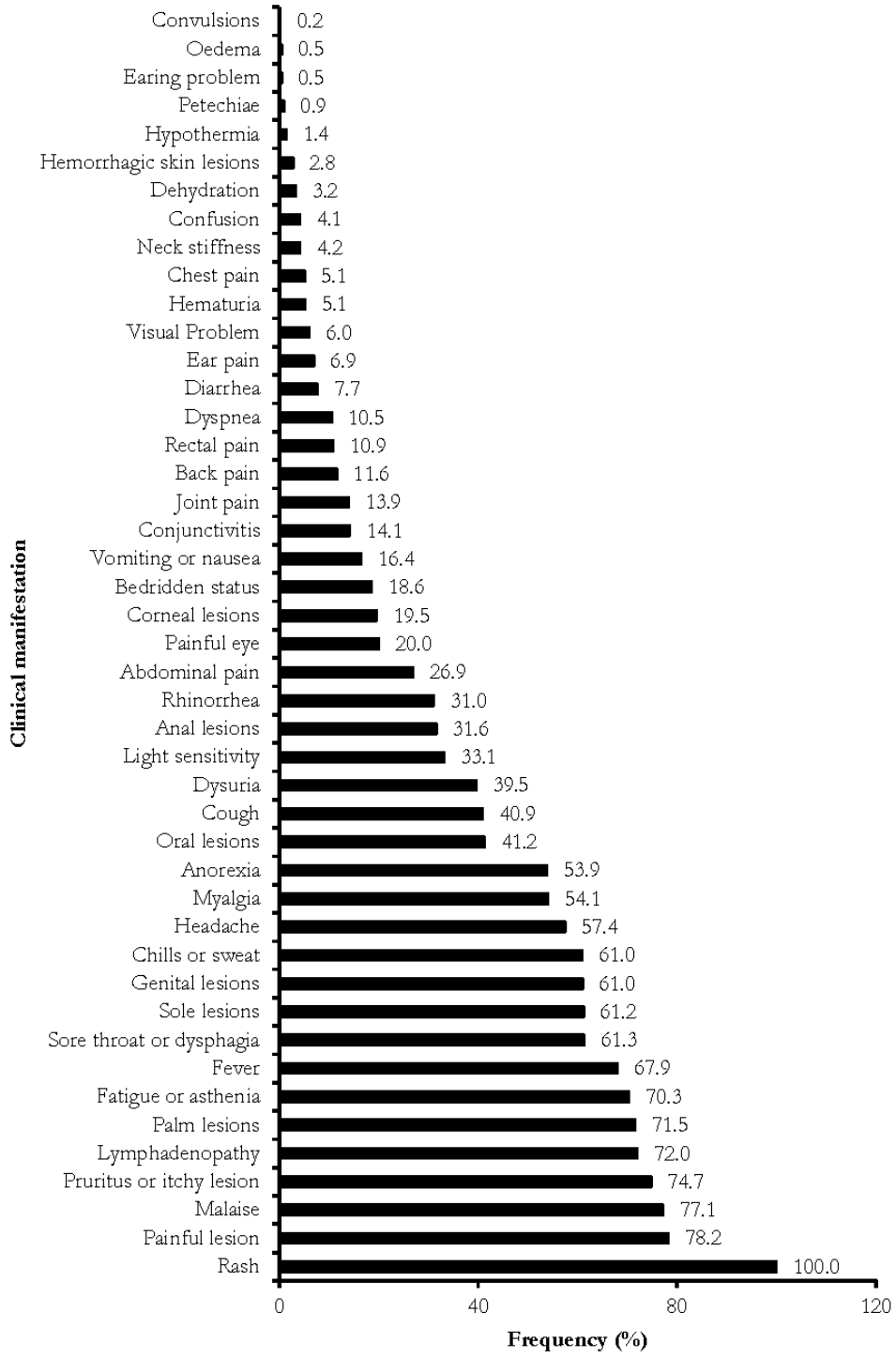

Figure 5: Trend of clinical manifestations observed among confirmed Mpox cases in DRC,1970–2024.

3.7. Meta-Regression Analysis

The multivariate analysis of suspected Mpox cases revealed a significant temporal increase in VZV prevalence (β = 0.2247, $p < 0.001$), while regional studies showed significantly higher VZV estimates than nationwide estimates (β = 4.7148, p < 0.001). For confirmed Mpox cases, regional studies had higher VZV estimates (β = 4.2220, $p = 0.018$). South Kivu exhibited significantly higher HIV coinfection 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 in either univariable or multivariable 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).

3.8. Publication Bias

The funnel plot asymmetry suggested a risk of publication bias for our study outcomes. The trim-and-fill analysis indicated the presence of four potentially missing studies, which did not substantially alter the pooled VZV prevalence among suspected Mpox cases, remaining at 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–Mpox coinfection, the trim-and-fill analysis suggested two potentially missing studies; however, their inclusion did not significantly alter the initial pooled rate of 0.52% (95% CI: 0.18–0.87) to 0.70% (95% CI: 0.00–1.60). (Supplementary Files S2–S4, Supplementary Figures S6 and S7).

3.9. Sensitivity Test Analysis

Sensitivity analysis of the pooled VZV prevalence among suspected Mpox cases demonstrated stable estimates (95% CI: 1.88–2.17%) when individual studies were sequentially excluded, supporting the robustness of the primary findings. However, exclusion of 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, potentially due to unique sample characteristics or methodological differences. Sensitivity analysis of the pooled VZV–Mpox coinfection rate also demonstrated stable estimates (95% CI:

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0.47–3.88 events per 100 observations) when most studies were sequentially excluded. Conversely, excluding the Kinganda-Lusamaki et al. study [16] increased the estimate to 11.66 events per 100 observations, highlighting its outlier influence on the pooled results. 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 S2; Supplementary Figure S8, Supplementary File S3; Supplementary Figure S7, and Supplementary Figure S8, respectively).

4. Discussion

4.1. Varicella-Zoster Virus-Mpox Coinfection

A pooled VZV coinfection rate of 9.69% was found in our meta-analysis among 1841 confirmed Mpox cases in the DRC. Significant heterogeneity indicated substantial variation among the included studies. Subgroup analyses provided additional information on these differences. Despite increased surveillance efforts in the later period, coinfection rates remained temporally stable, with comparable rates observed during 1991–2010 and 2011–2024. Regional variation was evident, with the Equateur region reporting a coinfection rate of 11.10% (six studies) and the Kivu region demonstrating a higher rate of 33.33% (single study).

The clinical similarities between VZV and Mpox rashes may result in diagnostic overlap and misclassification, particularly in settings with limited access to PCR confirmation [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].

The observed coinfection rates in this study were lower than those reported in studies from Nigeria, where 27–81% of confirmed Mpox cases were found to be 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].

VZV coinfection could be associated with greater disease severity and complications among confirmed Mpox cases in the DRC, consistent with findings from Nigeria, where coinfected individuals exhibited more complications than Mpox-only cases(56.3% vs. 22.5%, $p = 0.015$) [44]. In addition, in certain epidemiological contexts, rodents infected with poxvirus may transmit the disease via VZV skin lesions, potentially resulting in 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. To reliably differentiate between VZV–Mpox coinfections and single infections, the authors emphasize the need for dual diagnostic approaches, which may include PCR and serological testing [12]. Furthermore, due to their potentially more severe clinical presentation, coinfected patients may require additional care during hospitalization [44].

4.2. HIV-Mpox Coinfection

Among 1,652 confirmed Mpox cases, the HIV coinfection rate was 0.52%, with low heterogeneity observed across 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). These findings provide evidence that HIV–Mpox coinfection negatively affects clinical outcomes, including mortality [18]. Similar conclusions have been reported in a study from Nigeria [19].

4.3. Mpox Clinical Pattern

Rash, painful lesions, and malaise were the predominant clinical manifestations, suggesting that these symptoms should be incorporated into Mpox case definitions. 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 represents an important diagnostic marker for differentiating Mpox in endemic regions, despite being reported in only a single study. This result validates the DRC guidelines' inclusion of painful rash in clinical algorithms [1].

Differential diagnosis is further complicated by the predominance of systemic symptoms, such as fever and lymphadenopathy, which overlap with malaria, VZV, and other febrile illnesses 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 criterion [49].

This study underscores the need to broaden 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].

4.4. Strengths and Limitations

This review has several limitations. The limited number of included studies (<10) restricted the assessment of publication bias to the funnel plot, as conventional methods such as Egger's and Begg's tests could not be applied. Furthermore, the precision of the results was limited by wide confidence intervals due to small sample sizes in certain subgroup analyses. Nonetheless, the strength of this systematic review and meta-analysis lies in its provision of valuable insights into Mpox coinfection with other viral pathogens, such as VZV and HIV, in the DRC. The results emphasize the necessity of public health surveillance and actions to lessen and avoid disease complications among infected patients.

5. Conclusions

The clinical profile of Mpox in the DRC is characterized by an almost universal presentation of rash and frequent systemic symptoms, including malaise and painful lesions. This study also identifies inadequacies in the current case definitions and surveillance methods. There is a need for standardized, context-specific diagnostic methods that incorporate dual-pathogen testing and expand criteria to detect atypical presentations. This is highlighted by the considerable variability in symptom reporting and the significant rates of VZV coinfection. To enhance early detection and epidemic response in Africa's highest-burden settings, where Mpox remains a significant public health concern, these findings highlight the need for increased investment in laboratory capacity, healthcare worker training, and region-specific surveillance systems.

List of 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

Author Contributions

Conceptualization: F.Z.L.C.; Methodology: F.Z.L.C., C.A., W.N.B., and C.T.A; Data curation: F.Z.L.C.; Software: F.Z.L.C.; Validation: F.Z.L.C.; Formal analysis: F.Z.L.C.; Investigation: F.Z.L.C., C.A., and C.T.A; Resources: All authors; Writing—original draft preparation: F.Z.L.C.; Writing—review and editing: All authors; Visualization: F.Z.L.C. and W.N.B.; Supervision: F.Z.L.C.; Project administration: F.Z.L.C. All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

The data sources supporting this systematic review are available in the references. All data generated or analyzed during this study are included in this published article and supplemental material.

Conflicts of Interest

All authors declare no conflicts of interest.

Funding

The study did not receive any external funding and was conducted using only institutional resources.

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.

Acknowledgments

None Declared.

Supplementary Materials

Supplementary material associated with this article has been published online and is available at: https://doi.org/10.69709/ESHC.2026.183845.

AI Declaration

The AI tools (Gemini and Deepseek) were used to correct grammatical errors and ensure flow between different ideas presented in the text. The authors fully endorsed the content and findings in the present research article.

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