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Differential viral causes of vesicular rash in adults with suspected mpox in South Africa

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Summary

Since 2022, global mpox outbreaks have resulted in more than 130 000 laboratory-confirmed cases of mpox, with many occurring in countries considered non-endemic. Prior to the global re-emergence, mpox was a rare condition in humans, associated with few cases reported outside of central African countries. The rapid emergence of mpox has posed several challenges for accurate diagnosis and response to cases. The clinical recognition of mpox is problematic, partly due to a lack of experience with the clinical presentation of this disease and the wide differential diagnosis of vesicular rash with similar presentations. Here, we report the results from retrospective multiplex screening of samples submitted as suspected mpox cases in South Africa and identify other viral causes of vesicular rash.

Introduction

Mpox is a viral zoonosis caused by the monkeypox virus (MPXV), also commonly referred to as the mpox virus.[1] Prior to 2022, mpox was a rare disease in humans, reported sporadically from 11 countries in West and Central Africa.[2] Since 2022, a global outbreak has resulted in more than 130 000 laboratory-confirmed cases from more than 100 countries.[3] A large proportion of mpox cases reported from May 2022 until April 2025 were associated with the Clade IIb sublineage B.1.MPXV, a novel sublineage of MPXV that arose from sustained human-to-human transmission of the virus, initially in Nigeria and then beyond.[3-5] Since 2023, when it emerged from the Democratic Republic of the Congo (DRC), the Clade Ib variant of MPXV has continued to evolve in response to sustained human-to-human transmission.[6,7] Since 2024, there have been reports of mpox associated with Clade Ib MPXV from locations outside of the DRC.[3]

As reports of mpox continue despite efforts to contain its spread, shortages of mpox vaccines, the stigma which has become associated with the disease, and political instability in the DRC are a few of the factors that pose challenges to containing mpox, particularly in African countries.[8]

The MPXV is transmitted through close contact with the virus-laden lesions, scabs, or lesion fluid of infected individuals.[9] The virus may also be spread through contact with contaminated fomites and through large respiratory droplets, but these modes of transmission are not considered major drivers of mpox epidemics.[9] The most prominent feature of the disease is a painful vesicular rash.[10] The early signs and symptoms of the infection present as a non-specific febrile viral syndrome, and patients may complain of headache, muscle aches and a sore throat.[10] The skin rash develops typically within a week following illness onset and may vary greatly in severity.[10] The rash may be localised or more diffusely spread, and the number of lesions may be limited, or patients may also present with hundreds of lesions.[10] The case fatality rate of mpox varies from less than 1% to 10%, depending on the virus variant involved in the infection.[11,12] Clinical manifestation in immunocompromised patients, such as those living with unmanaged human immunodeficiency virus (HIV) infection, may be severe, increasing the risk of fatal outcomes.[12-14] The route of exposure may also influence

the presentation of the mpox rash.[12] In addition, it has been noted that the outcome of cases may also be subject to other factors, including the level of access to medical care and nutritional status, with malnutrition contributing to poor outcomes.[11,15] Surveillance bias, due to the greater likelihood of confirming cases in patients who sought medical care for their illness and in more severe (and hospitalised) cases of mpox, should also be considered, as it may inflate the case fatality rate when mild cases are not counted.[11]

The differential diagnosis of mpox is broad and may include diseases with infectious or non-infectious aetiologies.[12,16–18] Infectious diseases that may present with a rash similar to mpox include chickenpox, herpes simplex, syphilis, scabies, measles, bacterial and fungal skin infections, yaws, rickettsial pox, and other poxviruses such as molluscum contagiosum and variola.[19,20] Non-infectious causes of vesicular rash may include, but are not limited to, dermatitis herpetiformis, eczema herpeticum and insect bites.[21] The clinical recognition of mpox is challenging in the face of the broad range of differential diagnoses, occurrence of atypical or mild presentations, and a healthcare workforce that may be inexperienced in the recognition of the disease, given its historically rare occurrence. Thus, in addition to interrogating epidemiological history and risk factors, suspicion of mpox should ideally be confirmed by laboratory investigation.[17] The gold standard for mpox diagnosis is polymerase chain reaction (PCR) testing of samples derived from the skin lesions, typically swabs of the lesion sites. [22]

With the multi-country emergence of mpox, the disease has also been reported in South Africa since 2022. In South Africa, mpox is a Category 1 notifiable medical condition, with laboratory testing accessible through private laboratory services and the National Institute for Communicable Diseases (NICD), a division of the National Health Laboratory Service (NHLS). The NICD serves as the national reference centre for mpox. From June to August 2022, five cases associated with Clade IIb (sublineage B1.7) MPXVs were diagnosed. From May 2024 to August 2024, a further 25 mpox cases were diagnosed in South Africa. These cases were also characterised as Clade IIb but belonged to the B1.20 and B1.6 virus sublineages. Since February 2025, cases of Clade Ib-associated mpox have been diagnosed in the country.

To gain a clearer understanding of the differential diagnosis of mpox in the South African context, a retrospective cohort study was conducted. The study was focused on investigating other possible viral causes of vesicular rash in suspected adult mpox patients who tested negative for mpox.

Methods

Study design, cases and data source

A retrospective analysis of samples submitted for diagnostic investigation of mpox to the Special Viral Pathogens Laboratory (SVPL) of the Centre for Emerging Zoonotic and Parasitic Diseases (CEZPD), held within the NICD was performed.

Inclusion criteria

Residual samples received for mpox testing from 01 June 2024 to 31 October 2024 were included in the study. Only samples collected from adults (age 18 years and above) that tested negative by PCR for MPXV DNA were included in the study. Only samples collected from skin lesions (i.e., dry swabs or swabs in viral transport media) were included in the study. Blood, serum or other non-lesion material samples were excluded from the study, as these are not the preferred sample type for vesicular rash investigations.

Data source

This study used a Microsoft® Excel database, curated at the CEZPD, containing data pertaining to suspected mpox cases. The database was developed from data extracted from test requests and case investigation forms (available on the NICD website, www.nicd.ac.za) submitted with samples for mpox investigations.

Data extraction and analysis

A new spreadsheet was created with variables extracted from the mpox Microsoft® Excel database (see above) and included patient number, MPXV test result, date of test, and age and sex. The results of the multiplex PCR test for each virus target were additionally captured for the analysis. The results were summarised in frequency tables containing tallies and percentages.

Multiplex PCR testing

Homogenates prepared from clinical samples submitted for mpox testing were stored at 4–8°C and used for screening with a multiplex assay in this study. Clinical material for suspected mpox cases was processed using heightened biosafety control measures, i.e. segregation of equipment, use of disposable gowning, a double glove system, and N95 respirators.[22] The homogenates were prepared by transferring sample collection swabs to 400 µl phosphate buffered saline pH 7.4 (PBS) (Lonza, Switzerland) in separate microcentrifuge tubes. The tubes were briefly subjected to vortex mixing using a benchtop vortex mixer to improve the release of clinical material absorbed on the swab tips. Homogenate was used to process for routine nucleic acid extraction and MPXV PCR testing using in-house methods not described here.[23] For multiplex testing, the remaining homogenate volume was adjusted with the addition of 300 µl PBS. A total of 300 µl per sample was loaded into the main port on a QIAstat-Dx Viral Vesicular Panel cartridge (Qiagen, Germany). Loaded cartridges were fitted and run on a QIAstat-Dx Operating and Analytical Module (Qiagen, Germany). This is a fully automated molecular assay based on a single-use cartridge that includes all the reagents needed for nucleic acid extraction, multiplex PCR amplification, and the detection of all viruses (*orthopoxviruses,* including MPXV clade I, MPXV clade II, herpes simplex virus 1 (HSV-1), HSV-2, human herpes virus 6 (HHV-6), human enterovirus (HEV) and varicella zoster virus (VZV)). Amplification signals were analysed with the QIAstat-Dx Analyzer version 2.0. The QIAstat-Dx Analyzer automatically interprets results. Results for each of the eight viral targets were generated in approximately 70 min. The QIAstat-Dx includes an internal control and also generates Cycle Threshold (Ct) values for each target. The QIAstat-Dx assay is commercially available for research purposes only.

Results

Demographics of suspected mpox cases

For the period 01 June to 31 October 2024, 853 samples were received for 750 suspected mpox cases (multiple samples were submitted for some cases). The age, biological sex, and MPXV DNA test result category of these cases are summarised in Table 1. A total of 11 (1.5%) cases tested positive for MPXV DNA and were excluded. A total of 372 of 750 cases (49.6%) met the inclusion criteria listed above and were available for this study, while 378 cases (50.4%) were excluded based on the inclusion criteria listed above (i.e. age and/or sample type) (Figure 1).

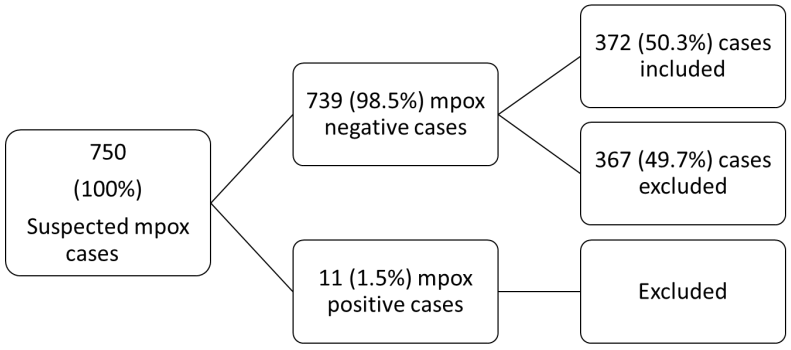

Figure 1. Visual representation of mpox case selection for this study. Of the 750 suspected cases received, 739 (98.5%) cases tested negative for mpox by PCR. Of these, 372 (50.3%) met the inclusion criteria and were further analysed.

Table 1. Age and sex* of suspected mpox cases for which samples were submitted for MPXV testing to the NICD/NHLS, South Africa, 01 June–31 October 2024.

	Sex number of cases (percentage of total)			Age range (percentage of total)	
	Male	**Female**	**Unknown**	**<18 years**	**18 years and above**
Cases testing positive for MPXV DNA (total number: 11)	11 (100%)	0	0	1 (9%)	10 (90.9%)
Cases testing negative for MPXV DNA (total number: 739)	475 (64.3%)	245 (33.2%)	19 (2.5%)	144 (19.5%)	595 (80.5%)

*As declared on the submission form or case investigation form.

Findings from multiplex PCR screening

A total of 52% (n=193/372) of MPXV DNA-negative cases tested PCR positive for other causes of viral vesicular rash when using the multiplex approach described here (Table 2). PCR positivity for two targets was detected in 18 cases. The co-infection profiles detected are presented in Figure 2.

Table 2. Cases testing positive for viral aetiologies of vesicular rash other than MPXV in suspected mpox cases tested at the NICD/NHLS, South Africa, 01 June–31 October 2024.

Target	Number of samples testing positive per target (percentage of total)	Number of samples testing negative per target (percentage of total)
Varicella zoster virus	174/372 (47 %)	198/372 (53%)
Herpes simplex virus 1	15/372 (4%)	357/372 (96%)
Herpes simplex virus 2	8/372 (2%)	364/372 (98%)
Human enterovirus	3/372 (1%)	369/372 (99%)
Human herpes virus 6	11/372 (3%)	361 /372 (97%)
Total (excluding dual infections)	193/372 (52%)	179/372 (48%)

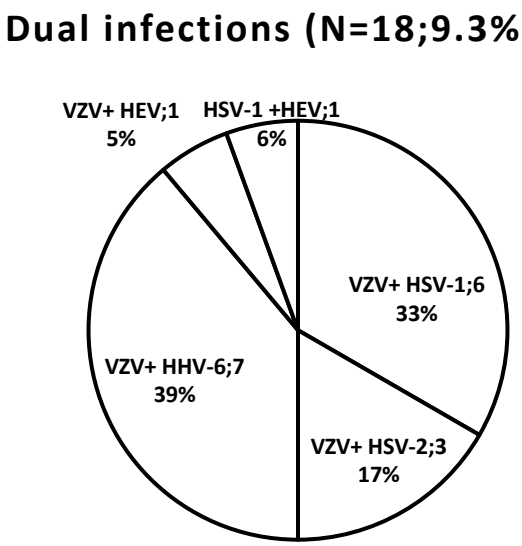

Figure 2. Co-infection profiles of the 18 cases testing positive for more than a single virus by multiplex PCR screening, South Africa, 01 June–31 October 2024.

VZV = varicella zoster virus, HSV-1 = herpes simplex virus 1, HSV-2 = herpes simplex virus 2, HHV-6 = human herpes virus 6, HEV = human enterovirus.

Demographics of cases testing positive for viral causes of vesicular rash other than mpox

Overall, twice as many PCR-positive results were found in males (132/193; 68.4%) compared to females (60/193; 31%), with only a single positive case of unknown sex (1/193; 0.5%) (Table 3). This distribution of positive results is reflective of the overall test submission rates for males (n=236/372; 63%) and females (n=135/372; 36.3%) meeting inclusion criteria.

However, amongst male submissions, the percentage detection of cases was higher (132/236; 56%) compared to females (60/135; 44%). Eighty-five per cent of infections were noted in an age demographic of under 40-year-olds, with approximately 54% detected in young adults between the ages of 18 and 30 years (Table 3).

Table 3. Age and biological sex of cases testing positive for viral aetiologies of vesicular rash other than MPXV in suspected mpox cases tested at the NICD/NHLS, South Africa, 01 June–31 October 2024.

Characteristic	Cases testing positive per target (percentage of total)				
	VZV	HSV-1	HHV-6	HSV-2	HEV
Sex*					
Male	117/193 (60.6%)	11/193 (5.7%)	9/193 (4.7%)	5/193 (2.6%)	3/193 (1.6%)
Female	56/193 (29%)	3/193 (1.6%)	2/193 (1%)	3/193 (1.6%)	0/193 (0%)
Unknown	1/193 (0.52%)	1/193 (0.52%)	0/193 (0%)	0/193 (0%)	0/193 (0%)
Total	174/193 (90.1%)	15/193 (7.7%)	11/193 (5.7%)	8/193 (4.1%)	3/193 (1.5%)
Age (years)					
18–30	94/193 (48.7%)	6/193 (3.1%)	8/193 (4.1%)	6/193 (3.1%)	1/193 (0.5%)
31–40	57/193 (29.5%)	3/193 (1.5%)	3/193 (1.5%)	0	1/193 (0.5%)
41–50	15/193 (7.7%)	4/193 (2.1%)	0	1/193 (0.5%)	1/193 (0.5%)
50–60	3/193 (1.5%)	1/193 (0.5%)	0	1/193 (0.5%)	0
>60	5/193 (2.6%)	1/193 (0.5%)	0	0	0

*As declared on the submission form or case investigation form.

VZV = varicella zoster virus, HSV-1 = herpes simplex virus 1, HHV-6 = human herpes virus 6, HSV-2 = herpes simplex virus 2, HEV = human enterovirus.

Discussion

The rapid emergence and global spread of mpox have posed several challenges for prompt diagnosis and response. The rare nature of the infection prior to 2022 resulted in a limited capacity for clinical diagnosis and a healthcare force that had little or no training or experience in the diagnosis of mpox. In addition, many infectious and non-infectious conditions may present similarly, which may further complicate accurate diagnosis. The increased number of mpox cases reported since 2022 and the so-called 'atypical' presentation of mpox, or rather, mpox dissimilar to what is historically reported, further impacts clinical diagnosis.

Here, we used a commercially available multiplex PCR assay to investigate possible viral aetiologies of vesicular rash in suspected mpox cases testing negative for MPXV at the NICD/NHLS, which primarily serves the public health sector in South Africa. More than half of the MPXV-negative samples tested positive for other viral targets. Similar retrospective analyses of sample submissions from clinically suspected mpox patients have yielded frequencies of 24–50% testing positive for at least one other vesicular rash-causing virus in MPXV-negative samples.[16,24-26]

Positivity for VZV was found in nearly half of the negative suspected mpox cases and was the most common differential diagnosis identified in this study. This finding is in keeping with reports from Kenya and Nigeria.[27,28] In similar studies conducted in Australia, Brazil, France, Italy, and Spain, lower levels of VZV positivity (3–22%) were found in MPXV DNA-negative samples from clinically suspected mpox cases.[16,26,29,30] Notably, the latter includes countries with routine varicella vaccination programmes.[31] In South Africa, vaccination against varicella is not part of the Department of Health's Expanded Programme on Immunisation (EPI) and is not available at public health facilities.

HSV-1 accounted for the second highest number of positives and was detected in 5.7% of negative mpox cases, with HSV-2 found in 4.1% of the cases. By comparison (although our case profile was predominantly male), the proportion of HSV-1 and HSV-2 DNA detection in an asymptomatic female South African cohort was reported at 9.6% and 5.6%, respectively.[32] Moreover, high prevalence rates for *Alphaherpesvirinae* (which includes HSV-1, HSV-2, and VZV) have been reported in South Africa. For example, Schaftenaar *et al.* reported seropositivity rates of 98% for HSV-1, 87% for HSV-2, and 89% for VZV.[33] By adulthood, most individuals have been exposed to HSV-1.[34] Similar to VZV, it also establishes latency and can be reactivated in vulnerable states, like immunosuppression.[33] It is often associated with HIV and other immunosuppressive diseases.[35,36] Hence, a reasonable explanation for the detection of *Alphaherpesvirinae* may be reactivation of latent virus, although primary infection could not be ruled out. In just under 10% of the cases, we noted dual infections of VZV and one other virus, most commonly HHV-6 and HSV-1. There are limited data on the co-infection of *Alphaherpesvirinae* and HHV-6. HHV-6 is a common childhood disease that establishes lifelong latency and is associated with opportunistic infections in immunocompromised patients (transplant recipients or unmanaged HIV cases).[37] Although rare, co-infections of VZV and HSV-1 have been reported in the literature.[38]

This study did not include samples from suspected cases of mpox in children. The differential for viral vesicular rash may be different in children; for example, a higher rate of positivity for enteroviruses – such as in cases of hand, foot, and mouth disease – may be expected. This study also did not assess any other non-viral causes of vesicular rash compatible with mpox, such as, but not limited to, *Chlamydia trachomatis*, *Neisseria gonorrhoea*, *Mycoplasma genitalium*, *Mycoplasma hominis,* and *Staphylococcus aureus*. The differential causes of vesicular rash in suspected mpox cases undertaken here are limited to the pathogens detected by the QIAstat-Dx Viral Vesicular Panel cartridge.

Conclusion

The results reported here support the usefulness of an integrated, multiplex approach for the laboratory diagnosis of viral vesicular rash. Given the frequency of other viral causes of rash in suspected mpox patients and the detection of co-infections, the multiplex approach may serve to enhance diagnosis and ultimately clinical management of the individual patients, as well as implementation of a more effective public health response.

Recommendations

- An integrated multiplex testing approach for viral causes of vesicular rash in suspected mpox cases is recommended. The benefit of multiplex testing for common viral causes of vesicular rash was demonstrated here. In addition, the value of integrated approaches for the diagnosis of sexually transmitted diseases presenting with vesicular or ulcerative rash could also be considered.
- Support for the healthcare workforce through training on the clinical diagnosis of mpox and vesicular rash is needed. In particular, distinguishing mpox from other causes of vesicular rash may affect patient care and clinical management and enhance public health responses in the context of optimal use of limited resources.

Conflict of interest

The authors declare no conflict of interest.

Ethical considerations

The reporting of this data was provided for by protocols approved by the Human Research Ethics Committee of the University of the Witwatersrand: *Evaluation and validation of molecular and serological diagnostic tools for the investigation of viral haemorrhagic fevers and rabies cases in South Africa*, M240479, and *Essential communicable disease surveillance and outbreak investigation activities of the National Institute for Communicable Diseases*, M210752.

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Disclaimer

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