Monkeypox outbreak in South Africa: Immunocompromised hotbed?

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South Afr J Health P 2025:8(1):e2480. https://doi.org/10.7196/SHS.2025.v8i1.2480

Keywords. Communicable diseases; Mpox; monkeypox; South Africa; disease outbreaks.

Monkeypox is a zoonotic viral disease, and an outbreak emerged in the Western Hemisphere in 2022. France, Germany, Portugal and the Netherlands reported cases of the disease.[1] However, global concern and media attention surrounding the virus subsequently dwindled as these outbreaks were swiftly controlled. More recently, emerging cases in the Southern Hemisphere, specifically in South Africa (SA), are cause for concern. The National Institute for Communicable Diseases (NICD) in SA has reported 25 cases and three deaths, indicating a case fatality rate of 12%.[2] SA has the highest absolute number of HIV-positive cases globally. Monkeypox is associated with a high mortality rate which, coupled with a large immunocompromised population, could create the perfect conditions for an unprecedented surge in cases in SA[1] – a concerning prospect.

History

Monkeypox was first identified in 1958 as a non-lethal 'smallpox-like' skin disease in research monkeys in Denmark.[3] The first human case was reported in a 9-month-old in the Congo (formerly Zaire) in 1970. Human Monkeypox virus (MPXV) cases have predominantly been endemic in Central and West Africa. The first zoonotic outbreak of human MPXV outside of the African continent occurred in the USA in 2003, following which there have been two major outbreaks in non-endemic regions, in 2021 and 2022.[4] Human MPXV cases outside of Africa have been associated with travel or animal importation. In May 2022, the World Health Organization (WHO) declared MPXV as a public health emergency of international concern. This status was reaffirmed in August 2024, when more than 45 000 confirmed and suspected cases were rapidly detected across Europe, America and all six WHO regions.[5]

Historically, the virus had a low case fatality rate (CFR). However, recent outbreaks have shown an increase in transmissibility, which could be attributed to recent mutations. MPXV cases have been managed by active surveillance, isolation and vaccination. In case of exposure, MPXV vaccination is advised for prophylaxis.

Virology

MPXV belongs to the Orthopoxvirus genus, which includes cowpox, vaccinia and smallpox. There are two strain groups of MPXV: the Central Clade I (sub-clades Ia and Ib) and West African Clade II (sub-clades IIa and IIb), with mortality rates of 10.6% and 3.6%, respectively. The 2022 - 2023 global outbreak has been linked to Clade IIb. The average age at diagnosis has risen from 4 - 21 years.[3-5] The term 'Monkeypox' is a misnomer, as African rope squirrels, tree squirrels, Gambian pouched rats and dormice are reservoir hosts, while primates are accidental hosts. Since the Smallpox vaccine is not included in the Expanded Programme of Immunisation, unvaccinated children and immunocompromised individuals are at a higher risk of acquiring the infection.[3]

MPXV is 200 - 250 nm with a brick-shaped structure. It comprises a lipoprotein core containing the viral genome, enzymes, lateral bodies and an outer envelope. It has a double-stranded linear DNA (~197 kb) that encodes around 190 non-overlapping open reading frames. These genes are involved in replication, virulence and host compatibility.[6] Owing to its double-stranded DNA, mutations are significantly lower. However, the 2022 MPXV diverged by 50 single nucleotide polymorphisms compared with the 2018-2019 virus, raising concerns about the acceleration of mutations.[5,7] The absolute implications of these mutations are yet to be understood, but this will serve as a base for new targeted vaccine development. MPXV spread in humans is predominantly higher from close contact with animals than from human-to-human transmission. Human-to-human transmission can occur through respiratory droplets and close contact with body fluids such as sexual intercourse.[8] The incubation period for MPXV varies from 5 - 21 days, after which clinical manifestations appear.

Signs and symptoms

MPXV is described as causing 'small-pox-like' skin lesions, with the most pathognomic clinical feature being the rash. The virus generally progresses through five stages. In Stage 1, lesions begin

as macules and last for 1 - 2 days. In stage 2, the macules progress to papules, lasting another 1 - 2 days. Stage 3 ensues when the papules evolve into vesicles, which last for 1 - 2 days. Stage 4 is characterised by pustule formation, where the blisters fill with puss and persist for about a week. Finally, in Stage 5, the pustules form scabs that ultimately fall off, lasting 1 - 2 weeks. The rash typically begins caudally on the face and traverses the umbilicus to spread to the soles of the feet. The chronological development of the full-blown disease from the initial infection can be divided into a prodrome and then a phase of the pathognomic rash. The initial symptoms include a headache, lethargy, fever, chills with/without sweats, sore throat (dysphagia), myalgia and lymphadenopathy.[9] Complications such as MPXV-induced encephalitis, keratitis, pneumonitis and bacterial infections may occur in patients infected with the disease. Of note, the differential diagnoses for MPXV include Varicella Zoster, herpes simplex, syphilis and other poxvirus infections.

Current situation in SA

SA has reported a total of 25 confirmed cases of MPXV between the 8th of May and the 25th of September 2024. These cases are located in three of the country's nine provinces: Western Cape, KwaZulu-Natal and Gauteng. The pertinent figure in this outbreak is the CFR, which stands at 12%, significantly higher than the international average of ~0.2% CFR. The increased CFR in SA is likely owing to a combination of factors including the stigma attached to such an infectious disease and the fact that all reported cases occurred in males aged 15 - 44 years. Notably, all the cases are among men who have sex with men (MSM), a group facing considerable stigma in traditional SA communities, which may further hinder access to healthcare. Most of the affected individuals are HIV-positive and/or live in close proximity to individuals who are newly diagnosed or have poorly controlled HIV. The unique HIV situation in SA contributes to the higher CFR compared with other regions, as the country has the highest number of HIV cases globally and such viral infections prey on the immunocompromised. All the patients were symptomatic and exhibited visible lesions. Sexual transmission is the primary mode of spread in SA. Genomic sequencing on five of the 25 cases has confirmed that this cluster is part of the sub-clade IIB MPXV outbreak.[10] All of the cases reported no history of travel, thereby indicating a local chain of transmission occurring within SA's borders. Contact tracing exercises are currently ongoing, and the SA authorities are working to curb the spread of the infection. Furthermore, leaders across the African continent are collaborating to address the outbreak. Tecovirimat, a WHO-approved drug, is being used and recommended by the NICD for severe cases. The fact that the spread of MPXV in SA is mainly through sexual contact among the immunocompromised, is cause for concern given the country's unique medical landscape and its global leading figures of HIV-positive cases. The South African Health Authorities have made a concerted effort to identify and respond to the outbreak. Governing agencies have procured MPXV vaccinations, with stockpiles scheduled to arrive in September 2024, to inoculate those most at risk.[11]

Conclusion

It is evident that the current MPXV outbreak occurring in SA is a significant concern both locally and internationally owing to its mode of transmission and high case fatality rate. If similar outbreaks were to occur in neighbouring countries with comparable immunocompromised populations, it could constitute a massive epidemic or even a pandemic. The manner in which the disease manifests in SA should raise global awareness, as the Northern Hemisphere is equally vulnerable to a similar event. Therefore, collaboration between different global agencies to effectively curb the spread is crucial. Immunisation campaigns must be initiated promptly to prevent further transmission and greater international support should be extended to Southern African countries to help combat the ongoing HIV pandemic.

Declaration. None.

Acknowledgements. The authors thank the Honourable Chairman, Mr. RPN Singh, and Prof. Dr. AP Singh, Sir Seewoosagur Ramgoolam Medical College, Mauritius for their constant support and encouragement.

Author contributions. JR contributed to the conceptualisation, writing of the original draft, data collection, data curation, investigation, methodology, resources, formal analysis, validation, visualisation and revising the draft based on reviewer comments.

AK conceptualised the study and contributed to the writing, data collection, data curation, investigation, methodology, resources, formal analysis, validation, visualisation and revising the draft based on reviewer comments.

IB contributed to the conceptualisation, writing of the original draft, data collection, data curation, investigation, methodology, resources, formal analysis, validation, visualisation, revising the draft based on reviewer comments and supervision.

Funding. None.

Data availability statement. Not applicable.

Conflicts of interest. None.

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Received 31 July 2024. Accepted 2 December 2024.