

Estimating the burden of mpox among MSM in South Africa

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ABSTRACT

Despite seeing few cases during the 2022–2023 mpox global outbreak, reports in May–July 2024 of 22 cases among men-who-have-sex-with-men (MSM) in South Africa, including three deaths, have raised concerns about under-reported community transmission. We used a Monte Carlo simulation model to estimate the true epidemic size, considering the increased severity of mpox among MSM living with advanced HIV, documented over-representation of people living with HIV among mpox cases and HIV prevalence in South Africa. We estimate that there have been between 220 and 450 cases among MSM LHIV in South Africa, with a total of 290–560 cases among all MSM. We provide an upper bound of 750–1600 cases as a sensitivity analysis where the prevalence of HIV among mpox patients is the same as population prevalence among MSM in South Africa. Estimates in both scenarios suggest a substantial number of undetected cases, with case ascertainment rates estimated between 1% and 8%. Our findings underscore the need for enhanced surveillance, targeted public health interventions and awareness campaigns to mitigate the outbreak's impact at a population level.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ 22 cases of MPXV Clade IIb among men-who-have-sex-with-men, including three deaths, in South Africa across May–July 2024 sparked widespread concern about undetected community transmission, given the low fatality ratio observed during the 2022–2023 global outbreak (0.15%–0.24%).

WHAT THIS STUDY ADDS

⇒ Using a simple probabilistic model which leverages the increased likelihood of a fatal outcome among people living with (advanced) HIV, it is estimated that the underlying epidemic size is likely larger than currently observed with a detection rate of between 1 in 14 and 1 in 100 cases.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Targeted public health interventions, such as increased surveillance in partnership with risk communication and community engagement, will be essential to manage future outbreaks effectively and mitigate their impact.

INTRODUCTION

Since 2022, the global outbreak of mpox has caused over 97 000 cases across 116 countries.¹ In contrast to outbreaks in historically endemic regions, transmission mostly occurred via sexual networks, with cases heavily concentrated among men who have sex with men (MSM).² Prior to 2024, South Africa was largely unaffected by the global outbreak of mpox, recording only five cases, all of which were linked to international travel.³ However, between May and July 2024, the country has reported 22 cases and three deaths.³ All 22 cases occurred in men aged between 17 and 43,⁴ most of whom self-identify as MSM (72% (13/18) among the cases reporting this information).^{5 6} Genomic sequencing was performed on a subset of five cases, all of which were confirmed to be MPXV subclade IIb—linking them to the 2022–2023 global outbreak, rather than the ongoing epidemic of MPXV clade I in the Democratic Republic of Congo and

bordering countries.⁷ The global outbreak of MPXV clade IIb has been associated with a low case fatality ratio (CFR) 0.21% (95% CI 0.15% to 0.24%),¹ so the three recent deaths in South Africa may represent only a small fraction of the underlying burden of mpox, prompting the need to understand the true number of cases—including those that remain undetected. Furthermore, the recent cases had no history of international travel or attendance at high-risk gatherings and are largely without epidemiological links, fuelling concern of sustained, undetected community transmission.^{5 6}

Globally, people living with HIV (PLHIV) have been disproportionately affected by mpox and are over-represented among both cases and deaths.⁸ Increased mpox severity and fatality rates among people living with advanced HIV (PLAHIV) have been well documented.⁹ The WHO characterises advanced HIV according to severely reduced CD4+Tcell counts (typically <200/mm³, in



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contrast to average levels of 800/mm³ in the general African population),¹⁰ which compromises the immune system's ability to fight infections. This heightened severity is of particular concern due to typically higher prevalence of HIV among MSM compared with the general population. South Africa is among the countries most affected by HIV worldwide, with an estimated 18.3% (95% CI 15.6% to 20.5%) of the adult population living with HIV, which rises to 29.4% (95% CI 25.5% to 33.5%) in MSM.^{9 10} At least two-thirds of the recent South African mpox cases occurred in PLAHIV—including the individuals with fatal outcomes.⁶

Reported cases are typically a subset of the true burden of infection of a particular pathogen.^{11–13} Statistical and mathematical modelling provide invaluable means by which to estimate unknown quantities of interest, such as the true burden of infections, by combining observed epidemiological data with existing knowledge about the pathogen of interest. Here, by leveraging the previously established relationship between deaths and cases via the CFR, we estimate the potential total number of undetected and undiagnosed mpox cases and deaths thus far (July 2024), accounting for the high prevalence of HIV in South Africa and its effect of mpox severity using a simple probabilistic model.

METHODS

To estimate the total number of mpox cases in MSM in South Africa, C , given observed deaths, all of which were in MSM living with advanced HIV (MSMLAHIV) ($D = D_{AHIV}$), we first calculated the expected number of cases among MSMLAHIV in South Africa, C_{AHIV} , using the corresponding observed mpox CFR among PLAHIV, $P(D_{AHIV} | C_{AHIV})$:

$$C_{AHIV} = \frac{D_{AHIV}}{P(D_{AHIV} | C_{AHIV})}$$

We then used this estimate to calculate the expected number of cases among all MSMLHIV in South Africa, C_{HIV} , by considering the proportion of mpox cases with of whose infection is in an advanced stage:

$$C_{HIV} = \frac{C_{AHIV}}{P(C_{AHIV} | C_{HIV})}$$

Finally, we estimated the total number of mpox cases among MSM in South Africa, using the prevalence of HIV among mpox cases:

$$C = \frac{C_{HIV}}{P(C_{HIV} | C)}$$

Model parametrisation

CFR in MSMLAHIV

A global case series of mpox among PLHIV found clear evidence of higher CFRs in people with lower CD4+T cell counts.⁹ Of the 27 mpox deaths recorded among a sample of 382 cases of HIV coinfection during the 2022–2023 global outbreak, 23 occurred in the 85 individuals CD4+T cell count <100/mm³, corresponding to a CFR of 27.1% (95% exact binomial CI 18.0% to 37.8%). The

remaining four deaths were recorded in the 94 individuals with CD4+T cell counts between 100 and 200/mm³, equating to a CFR of 15.1% (95% CI 10.2% to 21.2%) in those with CD4+T cell count <200/mm³. No deaths occurred in the 204/382 mpox cases with CD4+T cell count ≥200/mm³. The definition of 'advanced HIV' used in the South African mpox case reports is unclear but is defined by the WHO as CD4+T cell count <200/mm³, which we take as our central value. However, we perform sensitivity analysis using an alternative definition based on CD4+T cell count <100/mm³.

Proportion of mpox cases LHIV with advanced HIV

We assume that the proportion of MSMLHIV whose HIV infection is at an advanced stage is the same among mpox cases as in the MSM population, specifically, that the probability of having advanced HIV can be considered independent of the probability of having mpox, conditional on HIV infection. To quantify the proportion of MSM LHIV whose infection is in an advanced stage, we use estimates from the Thembeisa 4.7, a transmission-dynamic deterministic compartmental model of HIV in South Africa,¹⁴ which has been used to produce HIV estimates for national policy development including those reported by UNAIDS.¹⁵ The model predicts that 6.6% of adults living with HIV in South Africa in 2024 will have a CD4+T cell count below 200/mm³.

For our sensitivity analysis of the definition of 'advanced HIV', we assume that 3.3% of the population will have CD4+T cell count <100/mm³ (ie, that CD4+T cell counts are distributed roughly uniformly below 200/mm³). This assumption aligns with the global case series of mpox in PLAHIV, in which mpox cases with CD4+T cell counts <100/mm³ comprised 47.4% (n=84/179; 95% CI 40.0% to 55.1%) of mpox cases with CD4+T cell counts <200/mm³.⁹

Proportion of mpox cases LHIV

Globally, PLHIV have observed a higher incidence of mpox cases, likely due to shared sexual network risk.⁸ A conservative lower bound for the prevalence of HIV among mpox cases would therefore be the prevalence of HIV among MSM, $P(N_{HIV})$, which the Thembeisa model estimates at 29.5% (95% CI 25.5% to 33.5%) in South Africa. However, this method may overstate the overall number of cases so we consider this as a sensitivity analysis. Instead, our central scenario considers that the odds of LHIV given mpox infection are proportional to the odds of LHIV.

$$\alpha = \frac{\text{odds}(C_{HIV} | C)}{\text{odds}(N_{HIV})}$$

We estimated the OR, α , using mpox case data from the USA in which HIV prevalence was 56.4% (n=5350/9492; 95% CI 55.4% to 57.4%),¹⁶ compared with a prevalence of 12.4% (95% CI 10.9% to 13.8%) among all MSM.¹⁷ Serological evidence has shown a low prevalence of undiagnosed mpox in the USA, which supports the use of the data to form an unbiased assessment of risk patterns.¹⁸

Table 1 Model parameters, descriptions and sources

Parameter	Description	Distribution	Mean (95% CI)	Source
$P(D C_{CD4<200})$	Mpox CFR among PLAHIV	B(27, 152)	17.8% (10.2% to 20.7%)	⁹
$P(HIV_{SA})$	HIV prevalence among MSM in South Africa	B(146, 351)	29.4% (25.5% to 33.5%)	Thembisa V.4.7; ¹⁴ Beta distribution fitted via MOM
$P(HIV_{US})$	HIV prevalence among MSM in the USA	B(241, 1706)	12.4% (10.9% to 13.9%)	¹⁷ ; Beta distribution fitted via MOM
$P(HIV_{US} C)$	HIV prevalence among MSM with mpox in the USA	B(5350, 4142)	56.4% (55.3% to 57.3%)	¹⁶
α	OR of LHIV among mpox cases vs all MSM	NA	9.2 (8.0 to 10.6)	Estimated from the USA case data
Sensitivity analysis				
$P(D C_{CD4<100})$	Mpox CFR among PLAHIV	B(23, 62)	37.1% (18.2% to 36.9%)	⁹
α	OR of LHIV among mpox cases vs all MSM	NA	1	NA

CFR, case fatality ratio; LHIV, living with HIV; MOM, Method of Moments; MSM, men-who-have-sex-with-men; NA, not available; PLAHIV, people living with HIV.

These data suggest the odds of having HIV were $\alpha = 9.2$ (95% CI 7.9 to 10.6) times higher among mpox cases than in the general MSM population.

We multiplied the odds of HIV infection among all MSM by α to obtain a central estimate of the prevalence of HIV among mpox cases in South Africa:

$$P(C_{HIV}|C) = \frac{\alpha * odds(N_{HIV})}{1 + \alpha * odds(N_{HIV})}$$

Modelled scenarios

We created a Monte Carlo simulation model to quantify the potential number of mpox cases in South Africa (1) in MSMLAHIV; (2) in all MSMLHIV and (3) in MSM in total. Conditional probabilities were modelled using beta distributions, parameterised from the literature, either directly from reported sample numbers where possible or estimated via method-of-moments from mean and 95% confidence intervals (table 1). We generated 10 000 samples from parametric distributions to propagate the statistical uncertainty inherent in the parameter estimates throughout the calculations, allowing us to present results in terms of mean and 95% CIs. Analyses were performed in R V.4.2.2; model code is available at https://github.com/mrc-ide/mpox_sa.

RESULTS

Table 2 summarises the results of the central scenario and associated sensitivity analyses.

Estimated mpox cases among MSM LHIV

The three mpox deaths observed among PLAHIV in South Africa are consistent with an underlying burden of 21 cases (95% CI 15 to 29) (table 2). The 15 cases that have been observed in PLAHIV up to June 2024 are, therefore, broadly consistent with modelled expectations,

subject to case underascertainment. Taking the observed cases as a lower bound of the true total implies a case-ascertainment rate of 74.9% (95% CI 51.2% to 100%) among MSMLAHIV in South Africa. Under the assumption that 6.6% of HIV-positive MSM with mpox have CD4+T cell counts $<200/\text{mm}^3$, we estimate total cases in PLHIV in South Africa to be 313 (95% CI 227 to 444).

Estimated total mpox cases in MSM

Allowing for over-representation of PLHIV among mpox cases, in line with relative odds observed in the USA, suggests an HIV prevalence of 79.1% (95% CI 74.9% to 82.9%) among MSM with mpox in South Africa, compared with 29.4% (95% CI 25.5% to 33.5%) in all MSM. Taking this population prevalence of HIV into account, we estimate the total burden of mpox at 395 (95% CI 287 to 562) cases in South Africa. These estimates correspond to CFR at the high end of that observed in the global outbreak: 0.5%–1.0%, reflecting the high burden of HIV in South Africa and an mpox case ascertainment of around 3.9%–7.7% to date.

Sensitivity analyses

Using the alternative definition of ‘advanced HIV’ as CD4+T cell count $<100/\text{mm}^3$, the observed three deaths are compatible with 11 cases (95% CI 8 to 17) among MSMLAHIV in South Africa, which would imply that case ascertainment among MSMLAHIV has been extremely high, with 99.4% (95% CI 90.4% to 100%) of infections in this group already observed. Taking the 15 observed cases in PLAHIV as a lower bound for the true number of cases, the assumption that 3.3% of MSMLHIV have CD4+T cell counts $<100/\text{mm}^3$ is compatible with a higher number of cases than the CD4+T cell count $<200/\text{mm}^3$ definition, suggesting an underlying case burden of 458

Table 2 Estimated potential number of mpox cases in South Africa among MSMLAHIV, MSMLHIV and in total under four scenarios with corresponding parameter assumptions

Scenario:	Central	Sensitivity analyses		
OR of LHIV among mpox cases vs all MSM:	9.2 (8.0–10.6)	9.2 (8.0–10.6)	1	1
Definition of AHIV:	CD4<200/mm ³	CD4<100/mm ³	CD4<200/mm ³	CD4<100/mm ³
Observed D_{AHIV}	3	3	3	3
Assumed $P(D_{AHIV} C_{AHIV})$	15.0% (10.2%–20.6%)	27.1% (18.1%–36.8%)	15.0% (10.2%–20.6%)	27.1% (18.1%–36.8%)
Estimated C_{AHIV}	21 (15–29)	11 (8–17)	21 (15–29)	11 (8–17)
Observed C_{AHIV}	15	15	15	15
Assumed $P(C_{AHIV} C_{HIV})$	6.6%	3.3%	6.6%	3.3%
Estimated C_{HIV}	313 (227–444)	458 (455–503)	313 (227–444)	458 (455–503)
Assumed $P(C_{HIV} C)$	79.1% (75.0%–82.9%)	79.1% (75.0%–82.9%)	29.4% (25.5%–33.5%)	29.4% (25.5%–33.5%)
Estimated C	395 (287–562)	579 (549–640)	1068 (750–1543)	1565 (1361–1832)
Estimated $P(D C)$	0.78% (0.53%–1.05%)	0.52% (0.47%–0.55%)	0.29% (0.19%–0.40%)	0.19% (0.16%–0.22%)
Estimated cases detected	5.7% (3.9%–7.7%)	3.8% (3.4%–4.0%)	2.1% (1.4%–2.9%)	1.4% (1.2%–1.6%)

Results are presented as mean (95% CI) where applicable.

AHIV, advanced HIV; LHIV, living with HIV; MSM, men-who-have-sex-with-men; MSMLAHIV, MSM living with advanced HIV; MSMLHIV, MSM living with HIV.

(95% CI 455 to 503) among MSMLHIV and 579 (95% CI 549 to 640) in total in South Africa.

In the conservative scenario, where we assume that prevalence of HIV among mpox cases is in line with background HIV prevalence among MSM in South Africa at 29.4% (95% CI 25.5% to 33.5%), we estimate the total number of cases in the South African outbreak to be 1068 (95% CI 750 to 1543) if the reported deaths had CD4+T cell counts <200/mm³, or up to 1565 (95% CI 1361 to 1832) under the stricter definition of CD4+T cell counts <100/mm³. These figures are 2–3 fold higher than in the central scenario and are consistent with an overall infection fatality ratio of around 0.2%–0.3%, similar to that observed globally, and suggest that only 1%–3% of recent cases in South Africa have been detected.

DISCUSSION

Using reports from May to July 2024 of 15 mpox cases and 3 deaths among MSMLAHIV in South Africa, we used a simple probabilistic model to estimate the underlying burden of unobserved cases, both in total and among MSMLHIV during this period. The observed data, in conjunction with published estimates of the severity of mpox among PLHIV and PLAHIV, imply that only 1%–8% of cases from this outbreak have been reported. While observed cases rarely capture all infections for any pathogen, this substantial under-reporting of mpox could be attributed to several factors including, but not

limited to, lack of awareness in the community of mpox symptoms and risk factors for transmission, poor access to healthcare and fear of stigma associated with mpox and other sexually transmitted infections.¹⁹ Our pragmatic, statistical approach triangulates the data observed from the outbreak with the published literature on mpox epidemics to allow us to estimate the true outbreak size. Wherever possible, we have parameterised our simple model using data specific to South Africa, using estimates from other countries only where local estimates are unavailable. For example, it has been observed globally that the relative risk of HIV among mpox patients is higher than in the general MSM population, although the exact magnitude of this increased risk in South Africa is uncertain. To address this, we used data from the USA (where over 98% of cases among high-risk MSM were diagnosed,¹⁷ minimising the potential for reporting bias) to parameterise our model as a central estimate and presented sensitivity analyses bounding the potential range: at the lower end, assuming 100% HIV prevalence among mpox cases and at the upper end, assuming no increased HIV risk compared with the general MSM population. Although sociodemographic differences between PLHIV in the USA and South Africa likely influence the relative risk, the US-based estimate provides a conservative mid-point within this range.

Another key advantage of our model is the incorporation of context-specific factors, such as the high

prevalence of HIV among MSM in South Africa. A further strength is that we incorporate parametric uncertainty via the use of Monte Carlo simulations, allowing us to present a comprehensive view of the range of outcomes compatible with the observed number of cases and deaths. Finally, we present plausible upper and lower bounds for the true burden of mpox in South Africa by conducting a range of sensitivity analyses; we use different definitions of advanced HIV based on CD4 count thresholds, and present both cautious and neutral assumptions about the prevalence of HIV among mpox cases relative to the general population.

To enable estimation of the mpox case burden, we have made simplifying assumptions that should be borne in mind when interpreting the results. The uncertainty associated with each of these assumptions has been propagated through to our final estimates, which explains the relatively large confidence intervals that we report here. First, the accuracy of our results is dependent on any biases in published parameter estimates; for example, if many cases among PLAHIV have been undetected, then the CFR could be lower than estimated in the global case series,⁹ which would serve to increase estimates of case numbers presented here. Concerns around biased estimates of severity in PLAHIV are mitigated by the fact that mpox symptoms are also more severe in this population, suggesting ascertainment is likely high.⁹ However, it could also be the case that the true number of deaths from mpox is under-reported due to ambiguity in the documentation of causes of death, which may suggest the observed CFR is an underestimate. Second, given the case patterns observed globally, as well as recently in South Africa, our study limits the population at risk to MSM and does not consider transmission to other populations, such as female partners. Consequently, our estimates may be an underestimate of the full burden of mpox in South Africa. Third, we assume the severity of clade IIb mpox is unchanged since global outbreak, and that national differences in the observed CFR are attributable to the underlying prevalence of AHIV among MSM. Fourth, we assume that prevalence of AHIV is the same in mpox patients as among all MSM LWHIV—however, individuals with advanced HIV may be less likely to engage in sex, and so be less likely to contract mpox, compared with other HIV-infected individuals, which would also serve to increase estimates of the underlying number of cases. Moreover, recent studies have suggested that the percentage of men LAHIV in sub-Saharan Africa could be as high as 13%.²⁰ Adopting this higher estimate in our model would approximately halve the expected number of mpox cases. Conversely, LAHIV may make contracting mpox more likely if sexual contact with an infected individual does occur, due to inhibited mucosal immunity. Finally, we note that while information on the HIV status in the initial 20 cases was reported, this was not mentioned for the most recent two cases. We assume that these individuals are not LAHIV but note that if this were true then the estimated number

of mpox cases among MSM would increase. To place our findings in the broader context of global mpox outbreaks among MSM, in countries where epidemics have risen and peaked, likely due to a combination of network saturation effects and behavioural adaptation, the final epidemic size has been estimated to range from 0.1% to 1.5% of the MSM population,²¹ noting that determining accurate population denominators for MSM can be challenging. In South Africa, the MSM population is estimated at approximately 310 000 individuals,²² suggesting the potential final size of the mpox outbreak could reach up to 4650 cases, or 3–10× the current estimated size. This underscores the urgency for targeted public health interventions to manage the outbreak effectively and mitigate its impact such as increased surveillance in partnership with risk communication and community engagement to allow individuals to (a) know the risks of transmission and symptoms of mpox, (b) get tested and seek treatment if necessary and (c) consider changing their behaviour when engaging in activities associated with mpox transmission (eg, by using condoms or abstaining from sex while symptomatic). Although required in the acute phase of the outbreak, such measures should also be sustained in the longer term alongside improving access to healthcare for all individuals and reducing the stigma associated with mpox and other sexually transmitted infections.

CONCLUSIONS

A combination of evidence, including mpox cases without epidemiological links, history of travel or attendance at high-risk events/venues, coupled with three observed deaths, despite the low case fatality reported globally, suggests undetected community transmission of mpox among South African MSM. We find that the underlying epidemic size is likely larger than currently observed—corresponding to a detection rate of between 1 in 14 and 1 in 100 cases. Serological studies could confirm this, but in the meantime, enhanced surveillance, raising awareness, promoting testing, encouraging abstinence from sex while symptomatic and expanding vaccination efforts are critical to mitigating future transmission.

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