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Mpox (monkeypox) risk and mortality associated with HIV infection: a national case–control study in Nigeria

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ABSTRACT

Introduction Recent outbreaks of mpox are characterised by changes in the natural history of the disease, the demographic and clinical characteristics of the cases, and widening geographical distribution. We investigated the role of HIV and other sexually transmitted infections (STIs) coinfection among cases in the re-emergence of mpox to inform national and global response.

Methods We conducted a national descriptive and case–control study on cases in the 2017–2019 Nigerian mpox outbreak. Mpox cases were age, sex and geographical area matched each with two randomly selected controls from a representative national HIV/AIDS survey. Logistic regression was used to investigate the association between HIV infection and the risk of mpox acquisition and death.

Results Among 204 suspected mpox cases, 86 were confirmed (median age 31 years (IQR 27–38 years), mostly males (61 cases, 70.9%). Three-fifths of mpox cases had serological evidence of one or more STIs with 27.9% (24/86) coinfected with HIV. The case fatality rate was 9.4% (8/86) and 20.8% (5/24) overall and in HIV positive cases respectively. Mpox cases were more likely to have HIV coinfection compared with an age, gender and geography-matched control group drawn from the general population (OR 45 (95% CI 6.1 to 333.5, p=0.002) and when compared with non mpox rash cases (7.29 (95% CI 2.6 to 20.5, p<0.0001)). HIV coinfection and young age were associated with mortality among mpox cases (aOR 13.66 (95% CI 1.88 to 98.95, p=0.010) and aOR 0.90 (0.82–0.97, p=0.008), respectively).

Conclusion HIV infection was associated with a higher risk of contracting and dying from mpox. Children are also at high risk of death. STIs in mpox cases may be suggestive of high-risk sexual behaviours among these individuals.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The re-emergence of mpox in endemic areas has at least in part been attributed to reductions in population level immunity due to waning of smallpox vaccine induced immunity following its posteradication discontinuation while recent multi-country outbreaks suggest an increased risk due to close contact among sexual partners.

⇒ The age and geographical distribution of cases in Nigeria appear different from the recognised pattern in the Democratic Republic of Congo with cases occurring predominantly in adults in urban areas.

⇒ HIV infection may have a role in mpox acquisition, while the role of HIV associated immunosuppression on mortality is not unclear.

WHAT THIS STUDY ADDS

⇒ Our study provides further evidence of an increased risk of mpox infection among adults and mpox infection is independently associated with HIV-infection risk in an endemic setting.

⇒ We report a high mpox case fatality rate in HIV-infected individuals with a significantly increased odds of dying among coinfected cases and a high risk of children dying from mpox infection irrespective of HIV status.

⇒ While the association in this observational study cannot prove causation, these findings taken together with epidemiological data from the multicountry outbreaks suggests that sexual contact is an important factor in the re-emergence and transmission of mpox in Nigeria.

BACKGROUND

Human mpox is a smallpox-like illness caused by the monkeypox virus, and the most important *Orthopoxvirus* of global public health significance.[1 2] Following its first identification in the Democratic Republic of Congo (DRC) in 1970, there have been several outbreaks and sporadic cases across 11 African countries up to 2017.[3 4] The first occurrence of the disease outside Africa was in the USA in 2003 with 47 human cases attributed to close contact with prairie dogs believed to have been infected by rodents imported from Ghana.[5] Subsequently, four further cases outside Africa were

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Future studies and public health intervention should evaluate the role of contact in transmission and optimal vaccination strategies to protect high-risk groups.

⇒ The high prevalence of persons living with HIV who are not virologically suppressed and the HIV risk of mpox deaths provides further justification for the rapid scale up of antiretroviral therapy roll-out in endemic areas and for further research to investigate new effective medicines for mpox disease.

detected linked to the largest clade II monkeypox virus (previously called West African clade) outbreak between 2017 and 2018.[6–8] The current outbreaks of mpox in Europe and North America suggest the potential for further transmission in non-endemic settings.[9 10]

Despite some progress[11] over the last five decades, much remains unknown about the natural history, geographical and demographic distribution, determinants of disease severity and the true prevalence of mpox. There remains a need for enhanced surveillance and research targeted to inform recommendations by the WHO.[12–14] While mpox cases were previously commonly seen in children, recent outbreaks of the clade II have predominantly affected young adults in Nigeria.[6 8 15] Waning immunity from smallpox vaccination which provided cross protection against mpox is believed to be partly responsible for the recent resurgence.[13 16–22] However, this is not likely to explain the observed shift in age distribution of cases with current preponderance of young adults aged 15–40 years and mostly males in Nigeria who were born after the discontinuation of smallpox vaccination.[6] Additionally, most cases of mpox in Nigeria do not report contact with animals while >50% have a history of contact with persons with similar skin lesions. The clade II monkeypox virus was previously described as a less severe illness when compared with the Congo-basin clade, and with smallpox.[4 23] Nevertheless, a proportion of the cases in Nigeria were associated with adverse outcomes.[6 15] Consequently, further research is needed on the possible risk factors for mpox, and its severity as observed in recent outbreaks[9] including the role of immunity and coinfections.

A retrospective review of the hospital records of 40 human mpox cases from the Nigerian outbreak of 2017–2018 revealed that sexually active young adults were frequently affected.[15] The studies also noted that cases with HIV type 1 coinfection had more prolonged illnesses, larger lesions and higher rates of both secondary bacterial skin infections and genital ulcers compared with HIV-1 negative cases suggesting a possible role of HIV infection or immunodeficiency in the natural history and epidemiology of mpox.[15] Data from the 2022 multicountry outbreak have shown HIV prevalence to be as high as 41%–48% among mpox cases for whom status is known.[10 24–27] The association with immunosuppression is supported by evidence from animal experiments showing vaccination of severely immunodeficient macaques was not protective against a lethal monkeypox virus challenge, with development of innumerable pocks and resultant high mortality.[28] In addition, simian immunodeficiency virus infected and uninfected animals remained healthy at higher CD4+ cell counts and did not develop mpox lesions following virus challenge.[28]

As part of the national response activities to the 2017–2019 outbreak led by the Nigeria Centre for Disease Control (NCDC), we screened samples previously collected from mpox cases for HIV and three other sexually transmitted diseases namely human papillomavirus (HPV), syphilis and herpes simplex virus (HSV). With the aim of determining the role of HIV coinfection on mpox infection risk and disease severity, this study compared levels of HIV infection among mpox cases and age, sex and geographically matched controls drawn from a national representative survey[29] to determine whether HIV infection is more likely among those diagnosed with mpox. We also described the epidemiology of sexually transmitted infection (STIs) coinfections among mpox cases and investigated case fatality and the risk of death among mpox cases by HIV status.

METHODS

Study design and population

We conducted three case–control comparisons. First, we used data on all suspected and confirmed cases of mpox between 2017 and 2019 reported to the NCDC for which serum was available for HIV and other STIs screening. Cases were investigated using a standard epidemiological tool that collected information on age, gender, location of residence and whether the individuals died of mpox as part of national surveillance. Controls were selected from the National HIV/AIDS Indicator and Impact Survey (NAIIS) database domiciled at the National Agency for Control of AIDS. NAIIS was a national household-based survey that assessed the prevalence of HIV and related health indicators. The detailed procedures for this survey have been previously published.[29] In brief, data collection was from July to December 2018, within the period of the mpox resurgence in Nigeria. Data were collected from household members aged 0–64 years in all 774 local government areas in Nigeria.[29] The cases were compared with controls selected from the anonymised 2018 NAIIS database. Controls matched for age, gender and geographical location (state of residence) at the time of survey were selected at random from the NAIIS database. More than 70% of the mpox cases were in four of the 36 states and the Federal Capital Territory of Nigeria.[6 30] Selection of control by state level rather than at local government or settlement level reduces the effect of overmatching.

Second, we compared all confirmed cases of mpox with individuals with a rash who were suspected and found to have a negative confirmatory test (with or without an alternative diagnosis) to assess whether there is an

association with HIV status. Finally, we compared mpox cases who died with those who survived to determine the risk factors for mortality.

Sample size considerations

For the matched comparison of mpox cases and NAISS derived controls, using a 1:2 ratio of cases to controls, our matched analysis required 86 mpox patients and 172 matched controls to detect a 5-fold OR for HIV infection assuming a prevalence of HIV of 0.03 (based on NAIIS prevalence in geographical areas where the mpox cases were detected) using conditional logistic regression at a 5% significance level to achieve a statistical power of 80%. The sample size for the NAIIS survey was 172 603 (140 974 adults and 31 629 children)[29]

Laboratory investigation

We used a clade II -specific real-time PCR (RT-PCR) assay based on TaqMan technology[21] to confirm mpox cases. This is the gold standard for the confirmation of monkeypox virus infection. Archived blood samples from cases at the national reference laboratory were also tested for HIV, HPV, HSV and syphilis with appropriate serological tests. For both cases and controls, we used the three-test serial national HIV testing algorithm[31] which was also used for the 2018 NAIIS.[29 32] The serial rapid-testing algorithm utilises Determine HIV 1/2 (Abbott Molecular Inc., Des Plaines, Illinois, USA) as the first screening test. Non-reactive results were reported as HIV negative while positive tests were confirmed using Uni-Gold (Trinity Biotech, Wicklow, Ireland). If both results are concordant, a positive result is confirmed. For discordant results (Determine positive and Uni-Gold negative), the STAT PAK HIV 1/2 Assay (Chembio Diagnostic Systems, Medford, New York, USA) was used as the tie-breaker allowing reclassification to HIV positive or negative.

Syphilis, human papillomavirus (HPV) and HSV were tested using ELISA methods. Syphilis was tested with ELISA Ag Sandwich (Calbiotech ELISA); HSV 1&2 IgM, HSV IgG ELISA (Calbiotech) kits to test for HSV and HPV IgM ELISA Kit (Novateinbio) ELISA kits for HPV test.

Statistical analysis

All data analyses were carried out with STATA V.17. 0 (StataCorp). The demographic characteristics of the cases were summarised with descriptive statistics as well as the seroprevalence of the HIV, HPV, HSV and syphilis. Categorical variables were presented as frequency (and percentages) while age was presented as mean (SD). For the first comparison, using the age, sex and geographical location-matched cases and control dataset, a conditional logistic regression model was used to calculated OR (and their 95% CIs) to investigate the association between HIV status and monkeypox virus infection. HPV, HSV and syphilis were excluded in the model because of their non-availability in the control group. For the second comparison between confirmed mpox cases and suspected mpox with a negative test result, unconditional univariate and multivariable logistic regression was used to calculate OR for HIV infection adjusted for age and gender. Finally, to investigate the role of age and HIV status on mortality among confirmed mpox cases, unmatched multivariable logistic regression was used to determine adjusted ORs.[29]

RESULTS

A total of 204 suspected cases were tested for mpox with RT-PCR, of whom 86 (42.1%) were confirmed. The confirmed cases include 33, 40 and 13 cases seen in 2017, 2018 and 2019, respectively. Confirmed mpox cases were mostly male (61 cases, 70.9%), 73.2% (63 cases) were within the 21–40 years age group and these cases had a median age of 31 (IQR: 26–38) years. The age and sex distribution of the cases are shown in table 1. 54.5% (23/43 cases) had a known history of contact with persons with a similar rash prior to illness. Contact persons were household members, sexual partners, friends, colleagues, coinmates, neighbours or patients. There was no known history of contact with wild animals. Most cases (89.6 %) presented with genital lesions and 28.3% had oral lesions. Of the 86 confirmed mpox cases tested for HIV, 24 (27.9%) were seropositive and 54.1% (13/24) were males(figure 1). The seroprevalence of HIV in monkeypox virus negative participants was 5% (5/99) (figure 1). There were also five individuals with mpox-chickenpox coinfection, two of who had HIV coinfection.

Additionally, 60% of mpox cases tested for STIs were positive for one or more of HIV,[10] HPV,[22] HSV.[18] See figure 1 for details of the STI screening results. One HIV positive mpox case was concurrently positive for HPV IgM antibody and HSV-1 IgG antibody. HPV IgM antibody was present in 20 of 40 samples tested, HSV-1 IgG antibody was present in 18 of 80 samples tested, and HSV-2 IgG antibody was negative in all the samples tested. One mpox case had a positive HSV-1 Ig M antibody. All confirmed cases of mpox tested for syphilis were negative.

Table 1 shows the proportions of seropositivity of HIV infection among the mpox cases and the matched NAIIS controls with a prevalence of 27.9% (95% CI 18.8% to 38.6%) vs 1.7% (95% CI 0.36% to 5.0%) among cases and controls, respectively. The median age of HIV positive mpox cases was 30.5 (IQR: 27–38) years. For our main matched analysis using the conditional logistic model the OR for HIV infection among mpox cases compared with age, gender and location matched controls from the general population was 45 (95% CI 6.1 to 333.5.1, p<0.0001) .

For the second analysis, comparing confirmed mpox cases with other patients with a vesicular rash illness who had a negative mpox RT-PCR test as controls, the OR for HIV infection adjusted for age and gender was 7.29 (95% CI −2.6 to 20.5, p<0.0001) (table 2).

Eight out of 86 mpox cases died with a case fatality rate (CFR) of 9.4% (95% CI 4.1% to 17.5%). Five deaths were in HIV seropositive cases (4 adults and 1 child) with a CFR of 20.8% (5/24). Three deaths were in children aged 28

Table 1 Demographic, epidemiological and clinical characteristics of the studied mpox cases

	All mpox cases (%)	HIV positive mpox cases (%)	HIV negative mpox cases (%)
Gender			
Male	61/86 (70.9)	13/24 (54.1)	48/62 (77.4)
Female	25/86 (29.1)	11/24 (45.8)	14/62 (22.6)
Special population			
Children, <15 yreas	6/86 (7.0)	1/24(4.1)	5/62 (8.0)
Neonates	3/86 (3.5)	0(0)	3/62(4.4)
Inmates (prison)	2/86 (2.3)	0 (0)	
Cases by location			
South-South Zone	66 (76.6)	18 (75)	48 (77.4)
South-East Zone	8 (9.3)	0	8 (12.9)
South-West Zone	6 (7.0)	3 (12.5)	3 (4.8)
North-Central Zone	6 (7.0)	3 (12.5)	3 (4.8)
History of contact with persons with similar skin lesion (cases/frequency)			
Yes	23/43 (54.5)	7/11 (63.6)	16/32 (50)
No	20/43 (46.5)	4/11 (36.4)	16/32 (50)
Missing responses	43/86		
History of contact with animals			
Yes	1/35 (2.8)	1/12 (4.3)	0/23 (0)
No	34/35 (97.4)	11/12 (91.7)	23/23 (100)
Missing	51/86		
Fever			
Yes	46/55 (83.6)	19/20 (95)	27/62 (43.5)
No	9/85 (16.6)	1/20 (5)	8/62 (12.9)
Missing	31/86 (36)		
Lymphadenopathy			
Yes	34/46 (73.0)	13/16 (81.2)	21/24 (87.5)
No	6/46 (13)	3/16 (18.7)	3/24 (12.5)
Missing	46/86 (53.4)		
Hospitalisation			
Yes	47/58 (81.0)	19/20 (95)	28/38 (73.7)
No	11/58 (19.0)	1/20 (5)	10/38 (26.3)
Missing	28/86 (32.5)		
Bedridden			
Yes	11/48 (22.9)	6/16 (37.5)	5/32 (15.6)
No	37/48 (77.08)	10/16 (62.5)	27/32 (84.4)
Missing	38/86		
Case fatality			
Total deaths	8/86 (9.3)	6/24 (25)	2/62 (25)
Death in adults	5/80 (6.2)	5/23 (21.7)	5/57 (3.5)
Deaths in children (<15 years)	3/6 (50)	1 (100)	2/5 (40)

days, 5 and 11 years. The mean age at death from mpox is significantly lower than the mean age of survivors 22.5 years (22.5 (SD 15; 95% CI 9.9 to 35, p=0.025). The deaths occurred following hospitalisation in secondary or tertiary health facilities. HIV infection increased mortality with an age adjusted OR of 13.66 (95% CI 1.88 to 98.95, p=0.010) among coinfected compared with HIV seronegative mpox cases (table 3).

DISCUSSION

Our findings suggest a role for sexual transmission and HIV coinfection in the re-emergence of mpox in Nigeria,

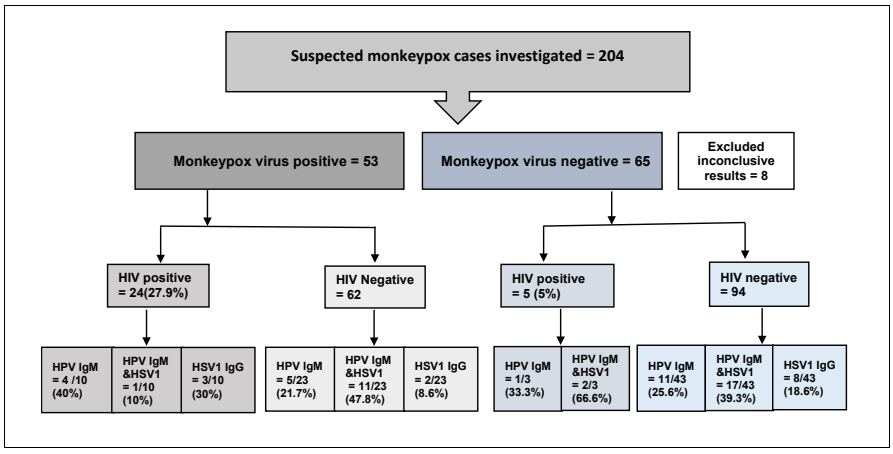

Figure 1 A flow diagram showing number of confirmed mpox cases and the seropositivity of HIV, human immunodeficiency virus; HPV, human papillomavirus and HSV, herpes simplex virus among the cohort of suspected mpox cases studied.

potentially contributing to the changing demography of affected population which could not be fully explained by wanning smallpox vaccine protection in the general population.[2 13] Our analysis further provides evidence for a high mpox case fatality among HIV infected individuals. While there is the need for further investigation, it is noteworthy that the Nigerian NAIIS, a nationally representative study during the same period as this study found that a high proportion of men living with HIV were unaware of their HIV status; an important determinant of linkage to care and consequently, survival. This might partly explain the high mortality in our series compared with settings with higher proportion on effective ART.[29]

Mpox was confirmed in 42.1% of the suspected cases with a male preponderance of 70.9% who were mostly in the 21–40 years of age. While the wanning smallpox immunity may explain the re-emergence of mpox in older individuals, children and adults under 40 were born after the discontinuation of smallpox vaccination. This may include close contact in high-risk sexual behaviours commonly associated with young adults.[33] The occurrence of serological evidence of one or more of HIV, HPV, HSV and Syphilis in three fifths of mpox cases supports the possibility of high-risk sexual behaviour in this cohort. About a quarter of mpox cases were coinfected with HIV; higher than the prevalence of HIV of 1.9% in the age, sex and geographical location matched controls resulting in a 45-fold increase in HIV among confirmed mpox cases compared with the general population. There was also an increased risk of HIV among confirmed mpox cases compared with suspected mpox cases with a rash illness. Assuming close contact during sex increases the risk of infection, the high proportion of males and HIV infection among mpox cases as well as the relatively high frequency of STIs may suggest a greater high-risk behaviour and sexual contact among men. These findings would be consistent with transmission patterns in the ongoing outbreak of mpox in non-endemic areas of the world predominantly among men who have sex with men.[9 10 34] The high proportion of females with monkeypox-HIV coinfection are at least in part explainable by the higher prevalence of HIV infection and a higher susceptibility to STIs among women in Nigeria.[32 35]

The risk of dying from mpox was nearly 14-fold higher in persons living with HIV compared with non-HIV coinfected cases. Given levels of antiretroviral therapy coverage between 2017 and 2019 when our study data were collected,[29] it is likely that the HIV individuals with adverse outcomes were not virologically suppressed. Furthermore, while mpox was uncommon in children, a high case fatality of 50% (3/6) in children in this study is concerning. The first of the three fatal cases presented as a neonate who had lost their mother to probable mpox, the second had a poorly treated HIV infection while the third had complications (encephalitis) at the time of presentation. These clinical presentations in these children and perhaps the very low number of cases reported in children would explain the very high fatality recorded in our study. Although lower than our findings, a higher

Table 2 Table showing logistic regression model for 86 confirmed mpox cases compared with 99 cases of rash illness who were suspected and found to have a negative confirmatory test

		Mpox cases (n=86)	Controls (n=99)	Univariate (OR; 95% CI; p value)	Multivariable (aOR; 95% CI; p value)
HIV	26 (27.9%) positive	24 (27.9%)	5 (5%)	7.27 (2.64 to 20.0); 0.001	7.29 (2.59 to 20.45); 0.001
Age (years)	Median (IQR)	31 (27–38)	29 (22–37)	1.02 (0.99 to 1.04); 0.095	1.01 (0.99 to 1.04); 0.210
Gender	n (% male)	61 (70.9)	69 (79.7)	1.06 (0.56 to 1.99); 0.855	1.22 (0.60 to 2.49); 0.569

Table 3 Table showing logistic regression model for predictors of mortality in a cohort of 86 mpox cases with eight deaths in Nigeria, 2017–2019

Variable		Died (n=8)	Univariate (OR; 95% CI; p value)	Multivariable (aOR; 95%, CI; p value)
HIV n (%)	Positive	5/24 (21)	5.17 (1.2 to 23.7); 0.034	13.66 (1.88 to 98.95); 0.010
	Negative	3/62 (4.8)		
Age (years)	Median (IQR)	28.5 (27–40)	0.94 (0.87 to 0.99); 0.34	0.90 (0.82 to 0.97); 0.008
Gender n (%)	Male	6/61 (9.8)	1.25 (0.23 to 6.7); 0.79	3.59 (0.54 to 23.6); 0.198
	Female	2/25 (8.0)		

case fatality of 4.2% in children under 5 years was observed in DRC compared with 3.4% in persons over 5 years.[36] These observations have implications for vaccination of high risk groups, and it is an important consideration in treatment target profiling of mpox therapeutic products. The high case fatality in HIV coinfected cases with mpox suggests the need to continue to scale up efforts towards achieving more voluntary HIV counselling and testing in the general population and the use of antiretrovirals in young adults living with HIV to achieve adequate viral load suppression. Additionally, there is a need for further research to identify mpox-specific antiviral agents.

Our study has a number of limitations. First, completeness of national surveillance data. Low case ascertainment may partly explain the high case fatality observed. Second, it is possible that frequent contact with health professionals among HIV infected persons, the high proportion of coinfected cases with genital lesions and the increase in disease severity in immunosuppressed individuals may alter care seeking leading to an over representation of HIV infection among mpox cases partly explaining the strong association in the risk of coinfection we observed. Unfortunately, our study is an extension of outbreak response and as such our data did not include CD4+ cell counts, viral load, and WHO classification, and antiretroviral treatment and adherence to it among the cohort studied. This has limited our capacity to extensively discuss the impact of these parameters that are known to impact on clinical status, disease progression and outcomes. Third, we were unable to compare levels of other STIs apart from HIV among controls because these infections were not routinely tested for in NAIIS. Therefore, it is possible that the observed higher level of HIV is simply a proxy of sexual behaviour rather than HIV-induced immunosuppression increasing the risk of monkeypox virus infection. Fourth, due to the small number of observed deaths, the estimated ORs from the logistic regression analysis on mortality had wide CIs. Other than these acknowledged limitations, we have no reason to believe there was a systematic bias in the identification of mpox cases or controls that influences the risk of prior HIV infection in this national study. NAIIS, the source of our control data, is the world's largest household HIV survey.[32] We adjusted for three important potential confounding variables—age, sex and geographical location. Future studies should assess levels of immunosuppression and aim to collect information on the risk factors for infection in endemic areas including contact with animals and population level and clinical cohorts with greater case ascertainment to better understand drivers of case fatality.

CONCLUSION

Our study has demonstrated a strong association between HIV infection and mpox risk and an increased risk of dying from the disease in people living with HIV which could be related to both high risk sexual behaviour and immunosuppression in this population. The preponderance of males among mpox cases and high levels of STIs may also point to a potential role of high-risk sexual contact predisposing to this disease. While the association in this observational study cannot prove causation, these findings taken together with epidemiological data from the multi-country outbreaks suggests that sexual contact is an important factor in the re-emergence/emergence of mpox. There is a need for further research to appropriately target therapeutic and preventive measures to groups such as those with a high-risk behaviour, HIV infection and children who may have an outsize risk of adverse outcomes.

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Contributors IA, CI, AY-O, MD and OA conceptualised the study. AY-O wrote the initial draft of the manuscript with oversight and input from CI and IA. AMA, AAh, AAd, IB and BO carried out laboratory sample analysis. AY-O, MD and FG extracted data. AY-O conducted data analyses. All authors reviewed the initial draft and provided input for revisions. All authors reviewed the final version and approved it for submission. AY-O accept responsibility for the conduct of the study and had access to the data.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval As part of the public health response to mpox resurgence in Nigeria, we obtained ethics waiver from the Nigerian National Health Research Ethics Committee (protocol number: NHREC/01/01/2007—8 February 2018; approval number—NHREC/01/01/2007—9 February 2017), to carry out further investigation on specimen from suspected and confirmed cases. Ethics approval was equally obtained for the NAIIS through the Nigerian National Health Research Ethics Committee and partners agencies' institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

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