Mpox in people with past infection or a complete vaccination course: a global case series

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Summary

Background Since May, 2022, a large global outbreak of human mpox (formerly known as monkeypox) has predominantly affected men who have sex with men. The strain responsible, Clade IIb, has mutated substantially from precursors originating from the 2017–18 outbreak in Nigeria. Immunity to smallpox, another orthopoxvirus, via previous infection or vaccination provides lifelong immunity. However, since the 2022 mpox outbreak, recent clusters were described in individuals with presumed immunity through recent infection or vaccination. We aim to describe the epidemiological and clinical characteristics of mpox in individuals with past infection or vaccination to improve the understanding of this disease in the setting of previous immunity.

Methods In this global case series, international collaborators from nine countries provided data on individuals with PCR-confirmed mpox after documented previous infection or vaccination between May 11, 2022, and June 30, 2023. We excluded cases that could not confirm vaccination status or cases with partial immunisation or any doses received before the current multi-national mpox outbreak (cutoff date May 1, 2022). Data were collected via a case report spreadsheet that reported on dates of infection and vaccination, route of immunisation, demographic characteristics, clinical findings, HIV status, concomitant sexually transmitted infections, and markers of disease severity (mpox severity score system). We describe case epidemiology, clinical course, and mpox severity scores; all analyses were descriptive.

Findings We report mpox infections in 37 gay and bisexual men who have sex with men: seven individuals had mpox reinfections, 29 individuals had mpox infections that occurred after two appropriately spaced Modified Vaccinia Ankara-Bavarian Nordic vaccine courses, and one individual had an infection that met the criteria for both reinfection and infection after vaccination. The median age of individuals was 36 years (IQR 30–45; range 21–58). Those with natural immunity after initial infection had a shorter disease course with less mucosal disease upon reinfection than with their initial infection. Infections post-vaccination were characterised by few lesions, little mucosal disease, and minimal analgesia requirements; two people received oral tecovirimat. Overall, there were no deaths, no bacterial superinfections, and all individuals were managed in the ambulatory clinic with one hospital admission for a necrotising neck lesion.

Interpretation The epidemiology of people with mpox reinfection or infection post-vaccination was similar to other published cohorts during the 2022 outbreak—predominantly young, sexually active gay and bisexual men who have sex with men. Clinical features and outcomes of repeat infection and infection after vaccination appear to be less clinically severe than those described in 2022 case literature. Specifically, compared with the 2022 case series, these individuals in the present study had fewer confluent lesions, less mucosal involvement, reduced analgesia requirement, and fewer admissions. Natural immunity and vaccine-induced immunity are not fully protective against mpox infection. However, in this small series both disease duration and severity appear to be reduced.

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Introduction

Since May, 2022, more than 87 000 cases of human mpox (formerly known as monkeypox) have been reported in 111 countries, leading to WHO declaring mpox a Public Health Emergency of International Concern (PHEIC) in July, 2022.[1,2] Unlike previously described outbreaks in historically affected countries, transmissions in the current multi country outbreak have predominantly affected sexually active gay, bisexual, and other men who have sex with men; transmissions have been associated with skin-to-skin and bodily fluid contact because human monkeypox virus (hMPXV) has been isolated from seminal, rectal, and vaginal secretions.[3,4] Infections in cisgender and transgender women have also been described.[5]

With respect to other orthopoxviruses, infection with the variola virus is known to confer lifelong immunity

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Research in context

Evidence before this study

Since May, 2022, mpox (formerly known as monkeypox), a disease caused by the orthopoxvirus human monkeypox virus (hMPXV), has caused outbreaks in 111 countries. Clade IIb, newly identified during the 2022 outbreak, has originated from subclade IIa but differs substantially both phylogenetically and clinically. Unlike previously epidemiological descriptions in historically affected countries, sexual networks of gay and bisexual men who have sex with men have been disproportionately affected during the current global outbreak. hMPXV has been isolated in semen as well as rectal and vaginal secretions and has shown to be replication-competent in the anorectum. Clear evidence of asymptomatic rectal carriage as well as case-pair data showing infectivity 4 days before symptom onset further strengthens the argument that mpox behaves as a sexually transmitted infection in the conventional sense. Some cases of repeat infections and infections after vaccination were reported in early 2023 in Europe and the Americas. Additionally, one case of phylogenetically confirmed reinfection has been described in detail. Taken together these findings warrant careful evaluation of the interplay between natural immunity and vaccine-induced immunity and reinfection with Clade IIb hMPXV. We searched PubMed for the terms "monkeypox, mpox AND (reinfection)" from May 11, 2022, to June 18, 2023. Publications were predominantly letters, perspectives, case reports, and public health agency reports. So far, case series of people with reinfection or infection post-vaccination have not come from more than a single centre or city and none have used a standardised severity scoring system to compare illness.

Added value of this study

This mpox case series is the largest and only series to describe both reinfections and infections after a complete vaccine course of Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN). Notably, both natural and post-vaccination immunity is considered lifelong in smallpox. Similarly, in Clade I and IIa mpox infections, reinfections, and post-vaccine infections have not been clearly described. We characterised 37 people with either reinfection after a previous infection in 2022, or an infection at least 14 days after a correctly administered complete course of MVA-BN since May, 2022. Compared with the severity scores documented earlier in the 2022 outbreak, the infections we described scored lower and were less extensive. When clinical features of a cases' repeat infections were compared with their first infections, these were also milder in severity. This assessment was based on reduction in mucosal involvement, confluence of lesions, analgesia requirement, and bacterial superinfection. Additionally, there were fewer hospitalisations than in several large case series already published. We also described one individual who received a complete vaccination course who went on to have a first infection 4 days later and a presumed second infection 266 days later following a documented mpox exposure.

Implications of all the available evidence

Our findings support the consideration that neither natural immunity from an initial mpox infection nor post-vaccination immunity are completely protective against the Clade IIb virus. However, the immunity from both appears to be of benefit in terms of limiting the most severe disease. Clinicians should be aware that previous infection and vaccination do not preclude mpox infection and they should maintain vigilance in making the diagnosis when clinical suspicion exists. Our small series reinforces the importance of vaccination and supports the recommendations that all people vulnerable to hMPXV infection should be prioritised for preventive mpox vaccination. This approach requires vaccines to be globally available in the countries historically affected by mpox and newly affected countries that still have no such access. Our study also reinforces that there is still much to learn about immunity with respect to the Clade IIb virus and ongoing phylogenetic, immunological, case-control, and randomised trial research is urgently needed. These efforts will need to include the collection of samples for virus isolation and sequencing to distinguish reinfection from relapse. There is also a need to bolster public health surveillance so that cases of suspected relapse, reinfection, and breakthrough infection should be notified to the relevant public health agencies to further inform policies and guidelines. How to safely protect immunosuppressed people, including people with advanced HIV disease, through vaccination is also a highly relevant area for research and for policy makers.

and the vaccinia virus vaccine is more than 95% effective in preventing smallpox infection.[6] Data from the multicountry outbreak have shown that hMPXV stimulates a robust immune response; this finding suggests that the benefit of vaccination within a year of infection might be limited.[7] Cases of non-Clade IIb mpox infections after childhood smallpox vaccination have been described previously.[8,9] So, the durability the protective immunity from either a previous infection or vaccination is worthy of further study. Furthermore, any possible role for viral persistence or latency in Clade IIb virus is also unclear. During the multicountry outbreak, several case reports have been published describing possible mpox reinfection.[10–14] Although not all infections have been confirmed through viral culture or phylogenetic sequencing, resolution of symptoms with interim negative mpox testing has been described in all cases. This finding is more clinically consistent with reinfection than relapse; however, the relapse cannot be completely excluded based on the evidence presented. One case of reinfection has been well described 3 months after initial infection in

an unvaccinated person with subtype IIb, lineage B.1 virus on both occasions based on whole-genome sequencing.[10] There is also evidence of other clades currently in circulation, raising further concerns regarding reinfection.[15]

Pre-exposure and post-exposure vaccination programmes have been a crucial part of the mpox response in North America and Europe. ACAM2000 (Sanofi Pasteur Biologics), a second-generation, replication-competent, single-dose smallpox vaccine and Modified Vaccinia Ankara Vaccine-Bavarian Nordic (MVA-BN; also known as IMVANEX, IMVAMUNE, or JYNNEOS), a third-generation, non-replicating, two-dose smallpox vaccine have been authorised for prevention of mpox in adults with MVA-BN predominantly being used currently. Although the effectiveness of ACAM2000 in preventing mpox has not been established, multiple studies have confirmed some degree of immunogenicity and a single study showed protection against mpox using its first-generation precursor, Dryvax (Wyeth Laboratories).[16,17] Throughout the current outbreak, effectiveness of MVA-BN has been studied largely through observational cohorts in real time and evidence of infection after vaccination has been reported.[18–24] More recently, discrete geographical mpox case clusters have been identified with 55–60% of infections occurring in people with previous infection or vaccination.[25,26] Complete vaccination with two doses of MVA-BN administered subcutaneously or intradermally 28 days apart was found to have an adjusted vaccine effectiveness of 86–89% in multiple observational cohorts.[20,21] Although the duration of vaccine efficacy remains unclear, these data have noted potentially less severe illness in mpox infection among vaccinated individuals.[27] However, these findings have been somewhat contradicted by a large case-control study, which adjusted for health-seeking behaviour, vaccination status, and calendar time, showing significantly lower estimated adjusted vaccine effectiveness rates of 35·8% after administration of one dose of MVA-BN and 66% after two doses.[19]

While data around vaccine efficacy are growing, little is known about the demographics and clinical manifestations of such breakthrough cases. Based on existing data, we hypothesised that mpox cases after past infection or vaccination, or both, might differ from cases with no past immunity already described in the literature. While WHO declared an end to the PHEIC for mpox in May, 2023, sustained transmission of Clade IIb virus has been established in humans, so the risk of resurgence remains a real public health threat. Building on the SHARE-Net international clinical network established at the beginning of the global mpox outbreak, we aim to report on mpox infections in a cohort from nine countries after previous infection or vaccination, and to describe the epidemiology and clinical presentations of these cases.

Methods

Study design

In response to new mpox case clusters disproportionately affecting people with presumed immunity, academic researchers within the London-based Sexual Health and HIV All East Research (SHARE) Collaborative (London, UK) renewed the international collaboration, SHARE-Net, co-led by the Section of Infectious Diseases and Global Health at the University of Chicago (Chicago, IL, USA). Researchers globally in locations with high

	Total number of individuals* (n=37)	Mpox case after past infection (n=8)	Mpox case after vaccination (n=30)
WHO region			
Region of the Americas	21/37 (57%)	5/8 (63%)	17/30 (57%)
European region	16/37 (43%)	3/8 (37%)	13/30 (43%)
Age, years	36 (30–45); 21–58	35 (31–37); 27–48	37 (30–45); 21–58
Gender			
Cisgender male	37/37 (100%)	8/8 (100%)	30/30 (100%)
Sexual orientation			
Gay	36/37 (97%)	8/8 (100%)	29/30 (97%)
Bisexual	1/37 (3%)	0/8	1/30 (3%)
Race and ethnicity			
White	28/37 (76%)	5/8 (63%)	24/30 (80%)
Hispanic or Latinx	4/37 (11%)	3/8 (37%)	1/30 (3%)
Asian	3/37 (8%)	0/8	3/30 (10%)
Black	2/37 (5%)	0/8	2/30 (7%)
Sexual partners in the past 30 days			
Multiple male partners	32/37 (86%)	6/8 (75%)	27/30 (90%)
Single male partner	4/37 (11%)	2/8 (25%)	2/30 (7%)
Multiple male and female partners	1/37 (3%)	0/8	1/30 (3%)
Type of sex in the past 30 days			
Oral and anal	34/37 (92%)	6/8 (75%)	29/30 (97%)
Anal only	2/37 (5%)	2/8 (25%)	0/30
Vaginal, oral, and anal	1/37 (3%)	0/8	1/30 (3%)
Condomless sex in the past 30 days			
Yes	35/37 (95%)	6/8 (75%)	30/30 (100%)
Not known	2/37 (5%)	2/8 (25%)	0/30
Participation in injection drug use for chemsex			
No	32/37 (87%)	7/8 (88%)	26/30 (87%)
Yes	3/37 (8%)	1/8 (12%)	2/30 (7%)
Not known	2/37 (5%)	0/8	2/30 (7%)
HIV status at most recent mpox diagnosis			
Negative	29/37 (78%)	3/8 (37%)	27/30 (90%)
Positive	8/37 (22%)	5/8 (63%)	3/30 (10%)
PrEP use in individuals not living with HIV			
Yes	24/29 (83%)	3/3 (100%)	22/27 (81%)
No	5/29 (17%)	0/3	5/27 (19%)
CD4 profile of individuals with HIV			
CD4 cell count at most recent mpox diagnosis, cells per mm^3	555 (363–979)	452 (296–852)	925 (662–1244)
CD4:CD8 ratio at most recent mpox diagnosis	0·70 (0·25–1·20)	0·32 (0·25–0·55)	1·05 (0·80–1·53)
CD4 nadir	355 (212–527)	212 (100–300)	527 (435–743)

(Table 1 continues on next page)

	Total number of individuals* (n=37)	Mpox case after past infection (n=8)	Mpox case after vaccination (n=30)
(Continued from previous page)			
Last viral load of those with HIV, RNA copies per mL			
<50	8/8 (100%)	5/5 (100%)	3/3 (100%)
Number of concomitant sexually transmitted infections at time of most recent mpox diagnosis			
0	25/37 (68%)	3/8 (38%)	23/30 (77%)
1	9/37 (24%)	5/8 (62%)	4/30 (13%)
≥2	3/37 (8%)	0/8	3/30 (10%)
Sexually transmitted infection present at time of most recent mpox diagnosis			
Gonorrhoea	6/37 (16%)	2/8 (25%)	4/30 (13%)
Chlamydia	6/37 (26%)	1/8 (13%)	5/30 (17%)
Syphilis	3/37 (8%)	1/8 (13%)	2/30 (7%)
Human papillomavirus disease, warts	1/37 (3%)	1/8 (13%)	0/30
Administration of childhood smallpox vaccine	3/37 (8%)	0/8	3/30 (10%)
Time between repeat infection, days	..	112 (42–221); 25–364	..
Time between MVA-BN doses, days	..	..	42 (31–62); 26–153
MVA-BN route of administration; dose 1, dose 2			
Subcutaneous, subcutaneous	..	..	14/30 (46%)
Subcutaneous, intradermal	..	..	8/30 (27%)
Intradermal, intradermal	..	..	8/30 (27%)
Time between vaccination completion and infection, days	..	..	219 (153–254); 49–315

Data are n/N (%), median (IQR); range, or median (IQR). MVA-BN=Modified Vaccinia Ankara-Bavarian Nordic. PrEP=pre-exposure prophylaxis. *One individual met criteria for both repeat infection and infection after vaccination, hence number of infections exceeds number of individuals included.

Table 1: **Demographics, sexual history, and vaccine status of cases**

numbers of mpox diagnoses were approached and invited to contribute to the case series. A convenience sample case series was collected to describe epidemiological and clinical features of mpox cases after past infection or vaccination between May 11, 2022, and June 30, 2023. Informed consent and local institutional review board approval for series inclusion was obtained and maintained in accordance with local standards and requirements. De-identified data were securely transferred, stored, and analysed at the coordinating site.

Case definition and identification

A confirmed mpox case after past infection was defined as a patient with clinically suspected mpox and PCR-confirmed infection, in a specimen from any anatomical site, with documented history of past PCR-confirmed infection and subsequent clinical recovery. A confirmed mpox case after vaccination was defined as a patient with clinically suspected mpox and PCR-confirmed mpox infection, in a specimen from any anatomical site, at least 14 days after documented receipt of two doses of MVA-BN administered after May 1, 2022. The window of 14 days was based on the time to protection guidance from the US Centers for Disease Control and Prevention.[28] We excluded cases that could not confirm vaccination status or cases with partial immunisation or any doses received before the current multi-national mpox outbreak (cutoff date May 1, 2022).

Data collection

Each contributing centre was provided with and completed a de-identified structured case report spreadsheet (CRS) adapted from prior SHARE-Net mpox case series.[3,5] As previously described, the CRS used drop-down menus and free-text fields to capture routinely collected data from electronic or paper medical records. This CRS focused on dates of infection and vaccination, route of immunisation, demographic characteristics, clinical findings, HIV status, concomitant sexually transmitted infections (STIs), and markers of disease severity. Sex and gender data were collected by self-report, and the options in the CRS were cis woman (assigned female at birth), trans woman (assigned male at birth), cis man (assigned male at birth), trans man (assigned female at birth), non-binary (assigned male at birth), and non-binary (assigned female at birth). The full CRS is in the appendix (pp 5–10).

Mpox Severity Score System (Mpox-SSS)

Since before the SHARE-Net collaborations, the Mpox-SSS has been developed as a validated tool to assess the spectrum of illness severity.[29] The Mpox-SSS includes seven unique elements: number of active lesions, anatomical extent of lesion involvement, presence of confluent lesions, presence of bacterial superinfection, extent of mucosal areas affected, level of care, and analgesia requirement (appendix p 4). Pilot data have shown the Mpox-SSS to be proficient in discriminating between more severe disease as well as adequately distinguishing change in disease severity over time.

Statistical analysis

All analyses were descriptive, and no hypothesis testing was done; data were analysed using SPSS Statistics (version 28). Aggregate or de-identified data are presented to avoid deductive disclosure. One individual's second infection met criteria for both repeat infection and infection after vaccination and was included in both groups for the analysis.

Role of the funding source

There was no funding source for this study.

Results

We identified eight cases with mpox infections after an initial infection and 30 infections after vaccination between May 11, 2022, and June 30, 2023, across nine countries and two WHO regions. Of the eight repeat infections, three (37%) were from the WHO European region (France and Italy) and five (63%) were from the region of the Americas (Argentina, Canada, Mexico, and

the USA). Of the 30 infections after vaccination, 17 (57%) were from the region of the Americas (USA) and 13 (43%) were from the European region (France, Israel, Spain, and the UK). Demographic and epidemiological characteristics of the cohort are shown in table 1.

The median age of included individuals was 36 years (IQR 30–45; range 21–58). 28 (76%) of the 37 individuals were White, and all identified as cisgendered gay or bisexual men. 32 (86%) of 37 reported having sex with multiple male partners and 35 (95%) of 37 reported inconsistent or no condom use. Three individuals also reported a history of recent injection drug use in the setting of chemsex. Eight individuals were known to be living with HIV; all were virologically suppressed (HIV viral load <50 RNA copies per mL) on antiretroviral therapy with a median CD4 cell count of 555 cells per µL (IQR 363–979; range 259–1389) and median CD4 nadir of 355 cells per µL (IQR 212–527; range 26–941). Of the 29 individuals who were not living with HIV, 24 (83%) were on HIV pre-exposure prophylaxis (PrEP). Of the entire cohort, 12 (32%) had at least one concomitant STI at the time of their mpox diagnosis. Regarding reinfections, the median duration of time between first and second mpox infection was 112 days (IQR 42–221; range 25–364). For post-vaccination infection, all 30 individuals completed an MVA-BN series with median of 42 days between doses (IQR 31–62; range 26–153) and 14 (46%) received both doses subcutaneously. The median time between completion of MVA-BN vaccination series and an infection meeting our case criteria (at least 14 days after second dose) was 219 days (IQR 153–254; range 49–315). Three individuals in the post-vaccination infection group had also received a childhood smallpox vaccination.

The clinical characteristics of mpox repeat infections are summarised in table 2. The presentation of the initial infection was with vesiculopustular rash (four [50%] of eight) or multiple ulcerations (four [50%] of eight); individuals with subsequent infections also presented with vesiculopustular rash (three [38%] of eight) and a single ulcer (two [25%] of eight). The median number of lesions was ten (IQR 3–17; range 2–30) in individuals with their first infection and five (IQR 1–16; range 1–50) in individuals with their second infection. Of the six cases with data available, the median duration of time between lesion appearance and resolution was 21·5 days (IQR 18–30; range 15–35) during their first infection compared with 15 days (IQR 5–20; range 5–21) with their subsequent diagnosis. The anogenital area was the most common anatomical site for both infections. No individuals required hospitalisation and none received mpox-specific antiviral therapy.

The median Mpox-SSS score decreased between first (7 [IQR 7–10]; range 3–12) and second infection (5·5 [IQR 4–7]; range 3–10; table 3). Although the median score for active lesion burden was the same, other parameters such as extent of body involvement, number

	Mpox after first infection		Mpox infection after two MVA-BVN vaccines (n=30)
	First infection (n=8)	Second infection (n=8)	
Type of rash			
Vesiculopustular rash	4/8 (50%)	3/8 (38%)	7/30 (23%)
Multiple ulcers	4/8 (50%)	3/8 (38%)	9/30 (30%)
Single ulcer	0/8	2/8 (25%)	12/30 (40%)
Umbilicated lesions	0/8	0/8	2/30 (7%)
Number of lesions	10 (3–17); 2–30	5 (1–16); 1–50	2 (1–5); 1–50
Duration of rash, days	21·5 (18–30); 15–35; n=6	15 (5–20); 5–21; n=6	14 (10–16); 5–21; n=15
Anogenital lesion present			
Anogenital mucosal lesions	2/8 (25%)	4/7 (57%)	4/26 (15%)
Anogenital skin lesions	4/8 (50%)	3/7 (43%)	15/26 (58%)
Both mucosal and skin lesions	2/8 (25%)	0/7	7/26 (27%)
Oral lesion present			
Mucosal lesions	3/3 (100%)	0	2/3 (67%)
Peri-oral lesions	0	0	0
Both	0	0	1/3 (33%)
Non-genital lesion present			
Trunk or limbs, or both	5/6 (83%)	2/2 (100%)	4/6 (66%)
Face	1/6 (17%)	0	2/6 (33%)
Ocular	0	0	0
Exanthem	0	0	0
Did the patient receive mpox anti-viral (tecovirimat)?			
No	6/6 (100%)	6/6 (100%)	28/30 (93%)
Yes	0/6	0/6	2/30 (7%)

Data are n/N (%) or median (IQR); range. MVA-BN=Modified Vaccinia Ankara-Bavarian Nordic.

Table 2: **Clinical characteristics of cases**

	Mpox after first infection		Mpox infection after two MVA-BN vaccines (n=30)
	First infection (n=8)	Second infection (n=8)	
Median score by category			
Active lesion burden, number†	1	1	1
Lesion burden, extent of body involvement‡	1·5	1	1
Confluent lesion or lesions with diameter >2 cm	0	0	0
Treatment for bacterial superinfection	0	0	0
Mucosal areas affected§¶	3	2	0
Level of care‖	1	1	1
Pain, analgesia requirement**	1	0	0
Overall score	7 (7–10); 3–12	5·5 (4–7); 3–10	5 (3–7); 3–11

Data are median or median (IQR); range. MVA-BN=Modified Vaccinia Ankara-Bavarian Nordic. *Each category ranges in score between 1 and 4; the sum of scores ranges from 1 through 23; full scoring system available in the appendix (p 4). †Includes only pox lesions. Healed lesions (scab absent and fresh skin present) not included. Rash from erythema multiforme or any other causes not included. ‡Includes each area as discrete area (head or neck; chest or abdomen; back; groin, buttocks, or anus; left arm; left hand; right arm; right hand; left leg; left foot; right leg; and right foot). §Includes each area as discrete area (anorectal; oropharyngeal; genital [solely mucosal]; and ocular). ¶Includes proctitis, urethritis,and oropharyngitis in the absence of lesions. ‖Highest level of care required (outpatient; inpatient, non-intensive care unit related to mpox; inpatient, intensive care unit related to mpox; and death). **Highest level of analgesia required (no pain medication; outpatient over-the-counter pain medication, including topical; inpatient, oral pain medication; inpatient, intravenous pain medications).

Table 3: **Mpox severity score system calculations***

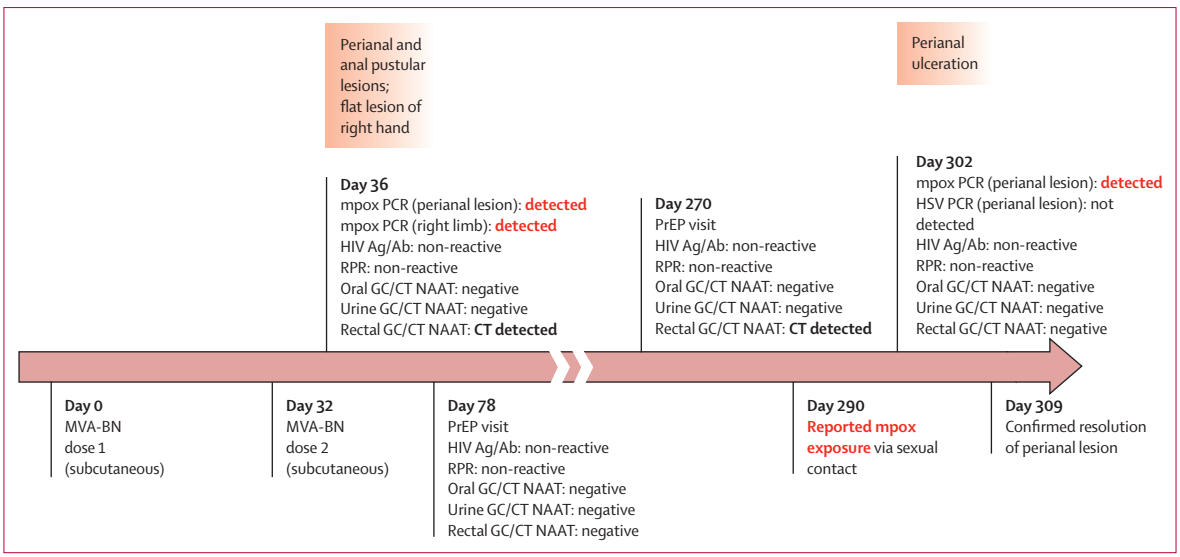

Figure: **Timeline of individual with mpox repeat infection and infection after vaccination**
This individual's second infection shown at day 302 met criteria for both repeat infection and infection of more than 14 days after receiving two doses of MVA-BN. Ag/Ab=Antigen/Antibody. CT=*Chlamydia trachomatis*. GC/CT NAAT=*Neisseria gonorrhoeae* and *Chlamydia trachomatis* nucleic acid amplification test. MVA-BN=Modified Vaccinia Ankara-Bavarian Nordic. PrEP=pre-exposure prophylaxis. RPR=Rapid Plasma Reagin.

of mucosal areas affected, and analgesia requirement were lower during the reinfection.

The clinical characteristics of mpox infections after vaccination are summarised in table 2. Most people presented with single ulcerations (12 [40%] of 30), multiple ulcers (nine [30%] of 30), or vesiculopustular rash (seven [23%] of 30). The median number of lesions was two (IQR 1–5; range 1–50) with a median duration of 15 days (IQR 10–16; range 5–21) before resolution. Lesions predominantly affected the anogenital region with the majority (15 [58%] of 26) not involving anogenital mucosal surfaces. Two (7%) people required mpox-specific antiviral therapy; both people were not living with HIV. One person required therapy due to swelling and pain from an oropharyngeal lesion and the other due to involvement of the neck necessitating hospitalisation. Both individuals received a 14-day course of oral tecovirimat with documented improvement.

Individuals with post-vaccination infections had a median Mpox-SSS score of 5 (IQR 3–7; range 3–11). Compared with repeat infections, individuals with infection after vaccination had numerically lower scores regarding extent of non-genital involvement, number of mucosal areas affected, and analgesia requirement.

One individual's second mpox infection met criteria for both repeat infection as well as infection more than 14 days after receiving two doses of MVA-BN (figure). This individual's first mpox infection occurred 4 days after the second vaccine dose. They presented with acute onset of anal and perianal pustular lesions and a solitary flat lesion on the hand; both locations were PCR-positive for hMPXV at the time of initial infection. The individual was not living with HIV and was taking PrEP. STI testing revealed rectal chlamydia for which the individual completed a 7-day course of doxycycline. Pain related to anal lesions was managed with over-the-counter non-steroidal anti-inflammatory analgesics. Precise duration of symptoms is not known; however, the individual returned for a PrEP follow-up visit 6 weeks later without any documented symptoms. Repeated swabs for hMPXV PCR were not performed.

The individual returned 266 days after his first infection (270 days after completion of vaccination) with a new painless perianal lesion following sexual contact (12 days before) with an individual with confirmed mpox. Examination revealed a perianal lesion thought to be an external haemorrhoid with two 1 mm ulcerations on its surface. The ulcers were swabbed and were PCR-positive for hMPXV. STI testing including herpes simplex virus PCR was negative; of note, he had screened positive for asymptomatic rectal chlamydia 3 weeks earlier and completed another 7-day course of doxycycline at that time. The perianal lesion resolved within 7 days of presentation; no over-the-counter or prescription analgesia was required. No subsequent PCR tests have been taken.

Discussion

Our case series is the first in the 2022 mpox global outbreak to focus on mpox infections both after previous infection and vaccination. The epidemiology of these infections mirrors that of the published series and cohorts of primary mpox infection early in the 2022 outbreak—all were in sexually active gay and bisexual men who have sex with men with multiple sexual partners. As with past cohorts, condomless sexual contact remained the primary route of transmission and a third of individuals had concomitant STIs diagnosed at the time of their mpox infection.

Clinical presentation of both repeat infections and infections after vaccination appeared to differ from the 2022 case literature on initial infections. The infections from the 2022 case literature had been characterised by evolution of painful pseudopustules at the anogenital areas with mucosal involvement in around 40% of cases as well as frequent debilitating oral lesions and commonly necessitated antibiotic treatment for bacterial superinfection.[3,5,27] In infections post-vaccination, solitary lesions were the most common presentation in our case series, whereas in the 2022 global case series only 10% presented as solitary lesion.[3] The anogenital area remained the most commonly involved site; although, mucosal lesions occurred less commonly than described in the 2022 case literature. There were no deaths in our cohort and all but one individual were managed in the outpatient setting. In the case literature in well resourced settings during the 2022 outbreak, 10–14% of individuals with mpox were hospitalised: of these, 11% for mpox-directed therapies, 30% for higher-level analgesia treatment, and 26% for treatment of bacterial super-infection.[3,6] In contrast, in this present case series there were no hospitalisations for bacterial superinfection or confluent disease.

The Mpox-SSS offered a new and objective means to compare severity and clinical outcomes of repeat infection and post-vaccinal infections. In reinfections, severity scores were lower between the first and second infection, which was driven by a lower number mucosal areas affected and reduced analgesia requirements. Similarly, in post-vaccination infections, the median severity score of 5 was lower than the published median score of 8 noted from the first 172 mpox cases retrospectively analysed from New York City.[29] The decreased Mpox-SSS was driven primarily by the absence of analgesia requirement and most individuals in the post-vaccine group did not require medication for pain.

Several limitations of our study should be highlighted. As an observational, retrospective, convenience case series including only PCR-confirmed symptomatic infections, selection bias might have occurred, because people with pauci-symptomatic or asymptomatic infections could have been missed leading to an underestimate of reinfections. Additionally, increased mpox disease awareness and improvement of time-to-diagnosis should be considered when comparing our results with data at the start of the current outbreak. As a case series reflecting real-life clinical practice, access and availability of hMPXV cycle threshold testing, viral load, genome sequencing, and immune response testing was not uniform, and was too haphazard to be analysed within our cohort in a meaningful way. The absence of virological characterisation as well as immunological data affects the ability to differentiate between reinfection and relapsed infection as well as define post-vaccination immunity. Future studies should consider inclusion of these tests to better characterise mpox after past infection or vaccination. Contact tracing was also not well documented so we were unable to provide this important information to better understand the potential for onward transmission. Finally, although this is the largest series to date, the small number of cases, especially with regard to repeat infections, should engender caution in the reader about overinterpretation of the results and their generalisability.

Overall, our findings suggest less severe mpox disease both in people with previous infection and in people who were vaccinated with MVA-BN than in the 2022 case literature. Our findings were characterised by diminished mucosal involvement and, probably relatedly, reduced analgesia, bacterial superinfection, and only 2·6% hospitalisation. These findings support the literature, signalling that vaccinations might reduce duration and severity.[26,27] Efforts to revitalise mpox vaccination campaigns continue in North America and Europe because sustained transmission in humans coupled with gaps in vaccine coverage, especially in racially minoritised communities, creates vulnerability for an mpox resurgence.[28] Consistent and clear interventions developed with and for affected communities to improve vaccination uptake are vital, as is further research to better understand vaccine effectiveness in preventing infection. Above all, ensuring equity of access to vaccines and treatments, specifically to geographical areas historically affected by mpox, must be prioritised if we aim to end this global outbreak and ensure elimination of human-to-human mpox transmission.

Contributors

AH and CMO conceived and designed the study. AH and CMO developed the case report form, coordinated the global collaboration, and managed the global data collection. AH, JZ, and CMO had access to, analysed, interpreted, and verified the data. All authors except EB, JF, and CMO submitted cases. AH, CMO, JZ, EB, and JF wrote the first draft of the manuscript. AH, JZ, and CMO edited the final draft. All authors reviewed the manuscript. All authors were responsible for the final decision to submit for publication and have seen and approved the manuscript. CMO, AH, and JZ had full access to all data.

Declaration of interests

We declare no competing interests.

Data sharing

De-identified participant data, including individual participant data, will be made available from the corresponding author on reasonable request.

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