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Letter to the Editor

Breakthrough monkeypox infection among individuals previously immunized with smallpox or monkeypox vaccination

Dear Editor,

recently in this journal Moschese D et al. and Orviz E et al. described the characteristics of the natural history of human monkeypox virus infection.^{1,2} Although it has been suggested that previous smallpox vaccination could be effective in preventing monkeypox infection, some cohorts support the evidence of breakthrough infections.³⁻⁷ Moreover, individuals belonging to key-populations are currently receiving vaccines licensed against monkeypox, but preliminary data suggest that administration of the second dose is crucial for the effective development of neutralizing antibodies.⁸⁻⁹

In this case-series monkeypox breakthrough infections following previous smallpox vaccination or recent single-dose monkeypox vaccination are presented.

Overall, 23 individuals diagnosed with monkeypox infection between June and September 2022 at the Infectious Diseases Unit of San Raffaele Scientific Institute, Milan, Italy, were included in this case-series: 20/23 (87%) previously received smallpox vaccination in their youth, 3/23 (13%) were recently vaccinated with one dose of monkeypox vaccination and were scheduled to receive a second one after 28 days.

Real-time (RT) PCR (RealStar® Orthopoxvirus PCR Kit 1.0 – altona DIAGNOSTICS) targeting the *variola virus* and the *non-variola* Orthopoxvirus species (*cowpox*, *monkeypox*, *raccoonpox*, *camelpox*, *vaccinia virus*) was used to detect *non-variola* DNA on swabs and serum, plasma, seminal fluids and urines samples and a specific RT-PCR targeting monkeypox virus DNA (Liferiver - SHANGHAI ZJ BIO-TECH CO., LTD) subsequently confirmed monkeypox infections.

Three individuals were taking HIV pre-exposure prophylaxis (PrEP), 18 were living with HIV, receiving antiretroviral therapy and with a CD4⁺ lymphocytes count >500 cells/microL and two were receiving immunosuppressive agents for other comorbidities.

Overall, 22/23 (96%) were men who have sex with men, 1/23 (4%) a transgender woman.

All reported high-risk sexual behaviours, most >10 partners in the three months prior to their monkeypox diagnosis and a past medical history of sexually transmitted infections and often chemsex use. Individuals' characteristics among those who previously received smallpox or monkeypox vaccinations are presented in Table 1.

Clinical presentation and course of disease were mild among all cases; only one individual living with HIV required hospitalization and antiviral treatment with cidofovir. All individuals achieved clinical resolution of symptoms and virologic clearance of infection, without negative outcomes.

Table 1

Individuals' characteristics among those who previously received smallpox or monkeypox vaccination.

Characteristics	Previous smallpox vaccination (n = 20)	Recent single-dose monkeypox vaccination (n = 3)
Age (years, IQR)	53 (50–57)	30 (28–32)
Living with HIV	16 (80%)	1 ((34%)
PrEP user	2 (10%)	1 (34%)
Previous STIs	18 (90%)	3 (100%)
Concurrent STIs	3 (15%)	2 (67%)
Number of sexual partners ^a (IQR)	10 (6–19)	10 (5–15)
Chemsex	6 (30%)	1 (34%)
Sexual contact with MPX case	8 (40%)	1 (34%)

Legend.

^a in the 3 months before MPX diagnosis; Abbreviations. IQR: interquartile; MPX: monkeypox; STI: sexually transmitted infection; PrEP: pre-exposure prophylaxis.

The median clinical duration of symptoms was 15 days (interquartile, IQR=11–21), which was apparently longer among individuals who previously received smallpox vaccination (16, IQR=12–22) than among who recently received a single-dose monkeypox one (6, IQR=4–8). The median number of lesions was 5 (IQR=2–12), which was similar among those who previously received smallpox vaccination (5, IQR=2–12) and those who recently received a single-dose monkeypox one (5, IQR=5–5). Presence of fever was reported among 14/23 (61%) individuals and lymphadenopathy among 12/23 (52%). Cutaneous involvement was recorded among 16/23 (70%), pharyngitis among 7/23 (30%) and proctitis among 12/23 (52%). Full details on monkeypox clinical presentations and course of disease are described in Table 2. Among individuals who recently received a single-dose monkeypox vaccination, the median time between vaccination administration and onset of clinical symptoms was 10 days (IQR=8–12).

This case-series corroborates the idea that breakthrough monkeypox infection can occur among individuals who previously received in their youth smallpox vaccination. Although it has been suggested that smallpox vaccination could be effective in preventing monkeypox infection, it is possible that the neutralizing antibodies which could grant this cross-protection likely diminish following several years from vaccination. For instance, the median age of the individuals who received smallpox vaccination in their youth was over 50 years. Notably, more than ¼ of individuals was living with HIV; we suggest that HIV-related immune-senescence and immunosuppression likely contributed in easing these breakthrough infections. Moreover, other individuals were taking immunosuppressive agents for co-morbidities, which also could have also played a role. Furthermore, we witnessed three monkeypox infections among individuals who were recently immunized with a single-dose monkeypox vaccination, with a scheduled second dose. These breakthrough infections are possibly caused by the short time between vaccination administration and infection,

Table 2

Clinical characteristics of monkeypox infection among individuals who previously received smallpox (Cases 1–20) or recent single-dose monkeypox (Cases 21–23) vaccination.

Cases	Lesions (n)	Fever	Lymphadenopathy	Pharyngitis	Cutaneous	Proctitis	Clinical duration (days)
Case 1	3	-	-	-	+	+	24
Case 2	1	-	+	+	-	-	20
Case 3	5	-	+	+	-	-	14
Case 4	6	+	+	-	+	-	17
Case 5	11	+	+	-	+	-	23
Case 6	32	+	+	-	+	+	23
Case 7	1	-	-	-	+	-	5
Case 8	3	+	+	+	+	+	21
Case 9	12	+	+	-	-	+	16
Case 10	22	+	+	+	+	-	15
Case 11	1	+	-	-	-	-	19
Case 12	5	+	-	-	-	+	12
Case 13	4	+	-	-	+	+	14
Case 14	3	-	+	-	+	-	16
Case 15	5	+	-	-	+	-	12
Case 16	20	-	-	+	+	-	32
Case 17	1	+	-	-	+	+	11
Case 18	20	+	+	-	+	+	12
Case 19	1	+	-	+	+	+	23
Case 20	5	-	-	-	+	+	8
Case 21	5	-	+	-	-	+	6
Case 22	5	+	+	+	-	+	4
Case 23	5	-	-	-	+	-	8

given the low titer of neutralizing antibodies expected following a single-dose administration.⁹ All in all, this case-series reinforces the idea that individuals previously vaccinated against smallpox require a booster dose and the need for administration of a full two-doses monkeypox vaccination for unimmunized individuals, together with providing adequate counselling, in a scenario of limited available data, on the possible risk of breakthrough infections.¹⁰

Declaration of Interest

None.

Contributorship statement

A.R.R., S.N. and C.C., visited the individual and contributed to writing the article. D.C., C.B. and E.B. visited the individuals and contributed to the reviewing of the article. A.C. coordinated clinical activities and contributed to the reviewing of the article. D.M. coordinated virologic activities and performed PCR tests for MPX. All authors have read and agreed to the published version of the manuscript.

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