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Comment

Monkeypox virus in human body sites and fluids: evidence for transmission

With more than 50,000 cases worldwide in since May, 2022, and more than 95% of them in men who have sex with men, the monkeypox outbreak continues to represent a major medical and public health concern. Uncertainties persist regarding the transmission routes; together with epidemiological data, new insights are expected from the virological evaluation of the presence of monkeypox virus (MPXV) in different areas of the human body.

In this issue of The Lancet Infectious Diseases, Romain Palich and colleagues report an extended evaluation of MPXV DNA in samples from skin, anus, throat, blood, urine, and semen from 50 French monkeypox cases. MPXV detection was more frequent in skin (44 [88%] of 50), anus (30 [71%] of 42), and throat (36 [77%] of 47) samples than from blood (13 [29%] of 45), urine (nine [22%] of 41), or semen (13 [54%] of 24) samples. Similar studies have been reported in the past months, with largely overlapping findings showing widespread viral detection in different areas of the body (table). The highest viral DNA loads were consistently found in skin (Cycle threshold [Ct] 19·8) and anogenital swabs (Ct 20·9), suggesting intimate sexual contact as the main route of transmission. This finding is supported by the data on semen, which frequently has shown as DNA-positive in patients with MPXV. Nevertheless, several questions regarding the contribution of the different bodily fluids to virus transmission need to be further addressed, also to better define the disease burden and the public health implications.

First, infectivity is a prerequisite for virus transmission. So far, virus isolation, whether in cell culture or animal models, is recognised as the only laboratory method to prove the presence of infectious viral particles in biological secretions. To date, evidence of replication-competent virus isolation has been reported only from skin (Cycle threshold [Ct] 19-8) and anogenital swabs (Ct 20-9), suggesting intimate sexual contact as the main route of transmission. This finding is supported by the data on semen, which frequently has shown as DNA-positive in patients with MPXV. Nevertheless, several questions regarding the contribution of the different bodily fluids to virus transmission need to be further addressed, also to better define the disease burden and the public health implications.

Second, clinicians remain unaware of whether the virus can persist within immune-privileged sites, and for how long. Palich and colleagues showed that viral clearance appeared to be relatively rapid, as most tested samples resulted MPXV-negative or weakly positive (below Ct 35) within 14 days after symptom onset. However, data are still scarce and to date MPXV detection and viral shedding kinetics, also in the prodromal stages, are largely unknown. For example, we know that related poxviruses have both primary and secondary viremias, but so far, MPXV viremia has only been assessed in late disease stages. Although poxvirus transmission with transfusion has been documented only once with smallpox, investigations are urgent, with potential implications for public health outside the current transmission chains (ie, in blood and tissue donations).

Finally, to better understand the biology, evolution, and spread of the virus causing the current outbreak, research efforts should be made regarding MPXV genome mapping and phylogenetic characterisation. Viral sequencing has refined phylogeny, with eight B.1 MPXV sub-lineages reported to date. A high number of mutations have been found in the viruses of the current outbreak, but whether these variations influenced
### Table: Large case series reporting prevalence of MPXV DNA and median Ct of positive samples at PCR in at least two different bodily fluids

| Participants | HIV Positive | Skin* | Anogenital | Urethra | Plasma | Fecal matter | MPXV DNA prevalence | Median Ct |
|--------------|--------------|-------|------------|--------|--------|--------------|----------------------|----------|
| France (Palich et al., 2022) | 50 | 22/50 (44%) | 44/50 (88%) | 20/42 (48%) | 30/42 (71%) | 21/42 (50%) | 23/42 (55%) | 31/42 (76%) |
| Spain (Peiró-Mestres et al., 2022) | 12 | 12/12 (100%) | 11/12 (92%) | 23/24 (96%) | 20/24 (83%) | 23/24 (96%) | 31/24 (100%) |
| 16 countries (Thornhill et al., 2022)† | 12 | 21/12 (175%) | 10/12 (83%) | 23/24 (96%) | 20/24 (83%) | 23/24 (96%) | 31/24 (100%) |
| France (Mailhe et al., 2022) | 264 | 73/256 (28%) | 252/258 (100%) | NA | NA | NA | 150/197 (76%) |
| Spain (Tarín-Vicente et al., 2022) | 181 | 72/181 (40%) | 178/180 (98%) | 43/55 (78%) | 82/117 (70%) | NA | NA |
| Italy (Raccagni et al., 2022) | 36 | 15/36 (42%) | 36/36 (100%) | NA | 22/36 (61%) | NA | 8/36 (22%) |

Data are n/N (%) unless otherwise specified. Ct=cycle threshold. MPXV=monkeypox virus. NA=not available. *Includes perianal skin. †Argentina, Australia, Belgium, Canada, Denmark, France, Germany, Israel, Italy, Mexico, Netherlands, UK, and USA. ‡Refers to skin or anogenital samples combined. §Refers to either skin, anogenital, or oropharyngeal samples combined.

MPXV transmissibility and virulence remains to be elucidated. Such notable diversification probably arises from long-term asymptomatic circulation leading to host adaptation, but previous smallpox vaccine-elicted immunity and different routes of transmission could also account for some of the phenotypic variations observed.

In conclusion, more extensive investigations are needed to obtain a coherent understanding of transmission factors that have permitted the extraordinary penetration of active MPXV infection into human communities worldwide. Notably, infection of animal hosts, including pets of confirmed cases or rodents infected by human stools in wastewaters, could further drive endemicity outside Africa. If this transmission continues, monkeypox cases are likely to increase in numbers outside of the community of men who have sex with men.

We declare no competing interests.

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