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Review

Monkeypox outbreak: Wastewater and environmental surveillance perspective

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HIGHLIGHTS

• MPXV DNA is excreted to wastewater from skin, nasal secretion, urine, and feces.
• Many infected persons could remain undetected with syndromic surveillance.
• Wastewater-based surveillance (WBS) can complement clinical surveillance of MPXV.
• Production of quantitative human MPXV DNA shedding data is critical.

GRAPHICAL ABSTRACT

ABSTRACT

Monkeypox disease (MPXD), a viral disease caused by the monkeypox virus (MPXV), is an emerging zoonotic disease endemic in some countries of Central and Western Africa but seldom reported outside the affected region. Since May 2022, MPXV has been reported at least in 74 countries globally, prompting the World Health Organization to declare...
1. Introduction

The spread of the monkeypox virus (MPXV) beyond its known endemic region has created a global public health challenge (CDC, 2022a; WHO, 2022a), leading to the declaration of a Public Health Emergency of International Concern by the World Health Organization (WHO) on July 23, 2022 (UN, 2022). The first human case of monkeypox disease (MPXD) was reported in 1970 in the Democratic Republic of the Congo (Yinka-Ogunleye et al., 2019). Subsequently, clinical cases have emerged around the rainforest regions of the Democratic Republic of the Congo and the rest of central and West Africa. Endemic circulation of MPXV occurs in central and western African countries, including Benin, Cameroon, the Central African Republic, the Democratic Republic of the Congo, Gabon, Côte d’Ivoire, Liberia, Nigeria, the Republic of the Congo, Sierra Leone, and South Sudan (Brown and Leggat, 2016; Hutin et al., 2001; Mbala et al., 2017; McCollum and Damon, 2014; Vaughan et al., 2018; Yinka-Ogunleye et al., 2018). The first MPXD outbreak outside of its endemic center (Central and West Africa) was reported in 2003 in the United States, with about 47 MPXD cases (Reynolds et al., 2006). The cause of that outbreak was linked to captive prairie dogs exposed to a rodent reservoir (Reed et al., 2004).

Since early May 2022, the number of cases of MPXD has rapidly increased outside the endemic regions (CDC, 2022a; Cohen, 2022; Peiró-Mestres et al., 2022; Tutu van Furfth et al., 2022). As of July 24, 2022, 16,836 confirmed cases of MPXD have been reported from 74 countries (CDC, 2022a). Of the confirmed cases, 98.6% (16,593) were reported from countries (68 out of 74 countries, or 92%) that have no previous reports of MPXV (CDC, 2022a). As of July 24, 2022, the five countries with the highest number of reported cases are Gibraltar (corresponding to 148.4 cases per million population), a British Overseas Territory near Spain, Spain (66.8 per million), Portugal (57.7 per million), Netherlands (41.6 per million), and Malta (38.5 per million). These numbers are continuously increasing every day and are updated timely on their official websites by WHO (WHO, 2022b), European Centre for Disease Prevention and Control (ECDC) (ECDC, 2022), and US CDC (CDC, 2022a). In this review, we shortly summarize aspects of MPXV outbreaks relevant to wastewater monitoring and discuss the challenges associated with wastewater-based surveillance (WBS).

2. Monkeypox virus taxonomy and transmission

MPXV is an enveloped, double-stranded DNA virus that belongs to the Orthopoxvirus genus of the Poxviridae family (McCollum and Damon, 2014; Vaughan et al., 2018). Viruses from the Poxviridae family are brick or oval-shaped, having eight genera, including Orthopoxvirus, Parapoxvirus, Molluscipoxvirus, Yatapoxvirus, Capripoxvirus, Suipoxvirus, Leporipoxvirus, and Avipoxvirus (Bonilla-Aldana and Rodriguez-Morales, 2022). The Orthopoxvirus genus contains many serological cross-interacting species, such as camelpox, cowpox, ectromelia, horsepox, monkeypox, raccoonpox, skunkpox, taterapox, usain gishu, vaccinia virus, variola (smallpox), and volepox (McCollum and Damon, 2014; Vaughan et al., 2018). MPXV has two genetic clades, the central African (Congo Basin) clade and the West African clade (Alakunle and Okeke, 2022; Bonilla-Aldana and Rodriguez-Morales, 2022). The Central African clade is considered to cause more severe symptoms and is more contagious (Alakunle and Okeke, 2022; WHO, 2022a). However, many people are against the clades naming convention (central African clade and West African clade) which is based on the geographic location of their first detection (Happi et al., 2022). As the virus does not respect geographic boundaries, naming an outbreak virus based on geographical locations is perceived as discriminatory and stigmatizing the people of those geographical regions (Happi et al., 2022).

Poxviruses are ubiquitous worldwide and cause widespread disease in humans and various animals (Alakunle and Okeke, 2022; Bonilla-Aldana and Rodriguez-Morales, 2022). These zoonotic viruses are transmitted to humans with direct contact through blood, bodily fluids, or cutaneous or mucosal lesions of infected animals, close contact with an infected person...
or animal, or physical contact with contaminated materials (Bonilla-Aldana and Rodríguez-Morales, 2022; WHO, 2022a). Further, eating inadequately cooked meat and other animal products of infected animals may increase transmission risks. Human MPXV infections historically arise from the animal-to-human transmission. Various animal species are susceptible to infection with MPXV. Animal hosts include a range of rodents and non-human primates. This includes rope squirrels, tree squirrels, Gambian pouched rats, dormice (Bonilla-Aldana and Rodríguez-Morales, 2022), different species of monkeys (Patrono et al., 2020), and other small mammals (Alakunle and Okeke, 2022). The natural reservoir of MPXV has not yet been identified, though rodents are believed to be the most likely.

3. Clinical characteristics, confirmation and treatment of MPXV

Mostly, the infection is self-limiting, with symptoms lasting from 2 to 4 weeks; however, it can be occasionally fatal (3-6% fatality rates) (Brown and Leggat, 2016). Major symptoms are fever, rash, and swollen lymph nodes, which may lead to medical complications (Ogina et al., 2020). Although the severity may relate to the extent of virus exposure, patient health status, and nature of complications, children and immunocompromised individuals can be more vulnerable to severe cases than healthy adults. The infection incubation period usually lasts 6 to 13 days but can range from 5 to 21 days (WHO, 2022a).

Many cases in the current outbreak are atypical of the classic clinical picture of MPXV infection (fever, swollen lymph nodes, followed by a centrifugal rash) (Brown and Leggat, 2016). Atypical features described currently include: presentation of only a few or even just a single lesion, absence of skin lesions in some cases, with anal pain and bleeding, lesions in the genital or perineal/perianal area which do not spread further, lesions appearing at different stages of development and the appearance of lesions before the onset of fever, malaise and other constitutional symptoms (WHO, 2022b). Clinical patients with such mild symptoms may not seek clinical treatments, so they can be out of clinical reporting. A recent study has reported three asymptomatic MPXV infected people while screening 224 chlamydia and gonorrhea patients and concluded that isolation of symptomatic individuals might not suffice to contain the outbreak (De Baetselier et al., 2022). Such asymptomatic infections are more likely to evade clinical reporting based on syndromic surveillance.

The CDC guideline recommends monitoring both non-lesion (e.g. urine and blood) and lesion materials (e.g. skin sample, vesicle fluid, crusts, and biopsy from infection) for clinical confirmation (CDC, 2022b). Clinical laboratories collect skin lesions, buccal and throat swabs, oral fluid, urine, and blood specimens for clinical confirmation (Leung et al., 2010; Tutu van Furth et al., 2022; Vaughan et al., 2018; Yong et al., 2020). Conventional tests that include virus isolation from a clinical specimen, electron microscopy, and immunohistochemistry are valid techniques. However, real-time quantitative polymerase chain reaction (qPCR) and digital PCR (dPCR) are preferred and available as sensitive methods (Leung et al., 2010; McCollum and Damon, 2014; Tiwari et al., 2022a; Ahmed et al., 2022).

Recently, the WHO reported a new vaccine has also been licensed to treat MPXV (WHO, 2022a). Vaccines based on the vaccinia virus have historically been used to prevent and eradicate smallpox. Now, the same vaccine (ACAM2000) has been shown to be effective in controlling MPXV (McCollum and Damon, 2014). This vaccine is based on live vaccinia virus preparation that is inoculated into the skin by pricking the skin surface. Antiviral drugs, such as tecovirimat (TPOXX) and cidofovir, could be treatment options for critically sick and immunocompromised infected individuals under the supervision of health care workers (McCollum and Damon, 2014). The prognosis of MPXV can be affected by multiple factors, such as previous vaccination status, initial health status, concurrent illness, and comorbidities. However, how the vaccination and drugs affect the virus shedding in infected individuals is limited.

4. Opportunities of wastewater surveillance for MPXV monitoring

Wastewater-based surveillance (WBS), based on monitoring of untreated wastewater, is an important approach for detecting emerging pathogens in communities, providing an opportunity for estimating spatial and temporal distribution, and circulating different variants of pathogens (Mao et al., 2020). Wastewater analysis has been widely used to monitor waterborne transmitted pathogens. Historically, it was used in the London cholera epidemic by the middle of 1800s, for tracking the fecal contamination of water pumps from nearby a cesspool (Johnston, 2006). The WBS is a critical component of the worldwide initiative to eradicate polio outbreaks (Aghar et al., 2014) and has recently been applied as a monitoring tool to fight globally against the COVID-19 pandemic (Ahmed et al., 2020; Ahmed et al, 2021a, b; Haramoto et al., 2020; Hokajärvi et al., 2021; Jakariyya et al., 2022; Kumar et al., 2020; Malla et al., 2022; Medema et al., 2020; Sherchan et al., 2022; Tiwari et al., 2022b). The same approach has been successfully used for monitoring many other pathogens including hepatitis E virus (Inconelli et al., 2020), rotavirus (Santiso-Bellón et al., 2020), adenovirus (Pong et al., 2010), hepatitis A virus (Hellmér et al., 2014), noroviruses (Hellmér et al., 2014; Prevost et al., 2015; Santiso-Bellón et al., 2020), JC polyomavirus (Levican et al., 2019), influenza A virus (Wolfe et al., 2022a), enteroviruses (Faley et al., 2022), canine picornaviruses (Faley et al., 2022), dengue virus (Thakali et al., 2022), metagenome markers of many other viruses including different poxviruses from the PoXVidae family (McCall et al., 2020), and antimicrobial resistant pathogens (Chau et al., 2022; Tiwari et al., 2022c), circulating in population level. Wastewater can be a perfect resource for monitoring communicable diseases outbreaks at a community level, as it comprises composite biological materials including lesion materials (e.g. skin, vesicle fluid, crusts), skin rashes, and various body fluids, including respiratory and nasal secretions, saliva, urine, feces, and semen of infected individuals (symptomatic, asymptomatic, pre-symptomatic, and post-symptomatic) in a community (Mao et al., 2020; Bibby et al., 2021; Sutton et al., 2022). WBS provides near real-time evidence for the shedding of infectious agents or their genetic components into the sewage system sometimes even several days before the onset of symptoms, and often before the infected person makes any contact to health care. Therefore, when clinical cases are laboratory confirmed and reported, it is possible that the circulation of a pathogen in communities may have already been detected with WBS (Bibby et al., 2021; Sutton et al., 2022).

With the global emergence of MPXV (CDC, 2022a, WHO, 2022a), robust epidemiological and laboratory surveillance systems are critical for efficiently targeting prevention and control measures for the areas and populations at risk. Combining the strengths of both clinical and environmental laboratory surveillance has the potential to strengthen the outbreak response at local, regional, and global levels. Clinical surveillance has some limitations and concerns, including social stigma, availability and cost of clinical testing, asymptomatic individuals not being reached, and so on (Sims and Kasprzyk-Hordern, 2020). Furthermore, clinical testing may not be able to account for the true prevalence of the disease as the infection is majorly self-limiting. Thus, infected individuals do not need to seek medical care and are not tested. Clinical testing is also limited due to possible zoonotic transmission in communities. WBS can overcome some of these limitations of the clinical monitoring approach. Table 1 shows the major strengths and disadvantages of clinical surveillance and the WBS approach for monitoring communicable diseases such as MPXV.

MPXV markers end in the wastewater from lesion materials (e.g. skin, vesicle fluid, crusts), skin rashes, and various body fluids, such as respiratory and nasal secretions, saliva, urine, feces, and semen of infected individuals (Leung et al., 2010; Tutu van Furth et al., 2022; Vaughan et al., 2018; Yong et al., 2020). For example, MPXV markers have been reported in semen, feces, and saliva in five MPXV-positive persons in Italy (Antinori et al., 2022). In another study in Barcelona, Spain, from 12 MPXV patients by Peiró-Mestres et al., MPXV was detected in saliva (12/12 cases), rectal swab (11/12 cases), nasopharyngeal swab (11/12 cases), semen (7/9 cases), urine (9/12 cases), and fecal samples (8/12 cases) (Peiró-Mestres et al., 2022).
et al., 2022). In addition, MPXV DNA has been detected in the urine and upper respiratory tract of clinical patients in the UK (Adler et al., 2022; Hobson et al., 2021). So far, only one study reported non-detection of MPXV DNA in the urine samples of infected individuals during clinical testing in the Netherlands (Tutu van Furth et al., 2022). Quantitative data on the shedding load of MPXV in samples from infected individuals have not yet been made available. Still, the DNA concentration in biological materials could be high enough, as the DNA from these materials was detected quite early in qPCR cycles (Peiró-Mestres et al., 2022; Wolfe et al., 2022b). Further, during bathing, MPXV scabbing skin lesions or defoliation of epithelial tissue and skin is an important shedding route to wastewater systems. Infected individuals may contribute MPXV to the sewage system through multiple routes; therefore, WBS can be a critical tool for monitoring infected cases and containment of the disease.

5. Early findings of WBS for MPXV monitoring

Currently, many laboratories around the world have started monitoring MPXV DNA in wastewater and tried to see the possible use of WBS of MPXV as its management tool. De Jonge et al. (2022) have recently reported the qualitative detection of MPXV in wastewater in five city districts in the Netherlands. They analyzed a total of 108 wastewater samples and monitored MPXV with the same USCDC assays G2R_G targeting the OPG002 gene and the G2R_WA assay (Wolfé et al., 2022b). The concentration of MPXV DNA with G2R_G target ranged from non-detected to 24,114 copies/g dry weight of wastewater solid. The reported virus concentration was 10^7-times higher in solid fraction of wastewater than in liquid fraction when considered by weight/mass (Wolfé et al., 2022b).

A next preprint study conducted in Miami-Dade County, USA reported 4675 and 6800 genomic copies/L detection of MPXV DNA and RNA from human infected cells in two hospital wastewater samples and five out of ten municipal wastewater samples (Sharkey et al., 2022). Another preprint study from Paris (France), reported an increasing trend in MPXV DNA in wastewater with early reported clinical cases of MXVD in the sewered communities (Wurtzer et al., 2022). They monitored a total of 264 samples collected earlier for WBS of COVID-19 with MPXV tagMan assay on the dPCR platform (Wurtzer et al., 2022). The next preprint from Rome, Italy, reported MPXV DNA from wastewater samples collected in airport buildings (La Rosa et al., 2022). They analyzed a total of twenty samples with qPCR and nested PCR by targeting the G2R region (TFN gene), F3L, and N3R genes. Three out of twenty samples were reported positive (La Rosa et al., 2022). All these recent studies have demonstrated that monitoring MPXV with WBS can be feasible, but the concept for MPXV monitoring is still at the proof-of-concept level. Most of these studies reported that MPXV levels in wastewater are relatively lower than SARS-CoV-2 levels reported elsewhere. Such a low detection rate of MPXV in wastewater needs to be investigated if this is due to a lower number of MPXV clinical cases or if MPXV is less abundantly shaded into wastewater (Sharkey et al., 2022). More data comparing MPXV clinical cases with the MPXV DNA data obtained from wastewater monitoring are needed to further validate the idea of WBS for MPXV. Recently, Chen and Bibby (2022) produced a model based on viral shedding and concluded the use of WBS for monitoring MPXV is theoretically possible (Chen and Bibby, 2022). However, their model, considered the MPXV DNA load in saliva, stool, and urine samples from an earlier published study on Chimpanzees (https://www.nature.com/articles/s41564-020-0706-0). Further, this
model has not included the possible variation of MPXV DNA in different infected individuals and the fate and decay of MPXV DNA in sewerage networks (Chen and Bibby, 2022).

6. Challenges of wastewater-based environmental surveillance for MPXV

There are some challenges in using WBS for monitoring MPXV in communities. The first challenge is the lack of standard procedures and methodologies, including sampling, virus concentration, DNA extraction, detection and data interpretation. As each virus has special characteristics, the most suitable method from the existing techniques must be selected. In some cases, it may not be appropriate to continue monitoring as developed previously. Further, the detection assay should be 100% inclusive, not cross-reactive with non-targeted species, and must not react with other Orthopoxvirus. For example, the currently used vaccine for MPXV, ACAM2000, is based on live vaccinia virus preparation that is inoculated into the skin by pricking the skin surface. After the vaccination campaign, the community spread of the vaccinia virus can be increased and could be detected in wastewater. Therefore, it should be considered carefully while developing and selecting the PCR assay for monitoring MPXV for WBS.

Second, information regarding virus DNA loads in symptomatic and asymptomatic carriers is currently unknown. The information about the release and load of the virus into the sewage system by infected individuals (symptomatic/asymptomatic), viral persistence, fate, and decay kinetics of such virus particles in wastewater under environmentally relevant conditions – are all critical for establishing a relationship between WBS data with clinical data. Unlike COVID-19 testing, MPXV can only be tested clinically if the patient has severe skin boils. In asymptomatic and mildly symptomatic cases, many people may not visit doctors, as the disease is self-limiting and would thus remain unreported. In addition, it may take time to develop severe boils after acquiring the virus. The lack of accurate data on MPXV infection makes it difficult to generate a prediction model or establish a relationship between clinical cases and WBS data (Chen and Bibby, 2022; Kiros, 2022).

Further, detecting the virus signal in wastewater may be affected by factors such as infection rate, process and analytical detection limits, wastewater flow, the complexity of the wastewater matrix, and shedding of the virus by infected individuals. To date, the persistence of MPXV in wastewater has not been documented, although one systematic review reported vaccinia virus persists for many days (first-order decay rate was reported – 0.15 per day) in freshwater and marine waters (Silverman and Boehm, 2021), indicating that MPXV also can be detected for days. Though it is a dsDNA genome virus, we can assume that the genetic material of the virus is relatively persistent, even when the viral envelope is damaged, and infectivity is lost. Further, there is a possibility of low signals of these viruses due to a low number of cases, as dilution of this virus can play a significant role for non-detects. Therefore, estimating the minimum number of infected individuals needed for detecting viral markers in sewage systems can be valuable in establishing methodological limits (Tiwari et al., 2022b).

Since monkeypox is a zoonotic virus, possible virus release from animal reservoirs to sewage systems could confound WBS data interpretation for human cases. However, zoonotic pathogens are mainly managed with a One Health approach (Bird and Mazet, 2018). This means if zoonotic pathogens are detected in any of the compartments, i.e., human, animal, or environment, it can jump from one compartment to the next, so the prevalence of the virus in one compartment can pose a risk to others. Therefore, the prevalence of zoonotic agents such as MPXV needs to be investigated simultaneously in all possible compartments. Thus, neither clinical surveillance nor wastewater surveillance alone can estimate the prevalence of zoonotic carriers in communities.

Further, the likelihood of virus transmission from water matrices is unknown. Viruses originating from skin defoliation can still be infective in wastewater, but their risk to public health and animal health remains unknown. Notably, the risk of direct infection from wastewater highlights that unknowns or different transmission routes can greatly influence the application of surveillance techniques. However, detection of virus DNA alone in the sewage system does not guarantee the presence of infective viral entities particles (Ahmed et al., 2021a,b; Tiwari et al., 2021; Tiwari et al., 2022b). Thus, more work is needed to assess MPXV infectivity in wastewater and determine MPXV viral DNA load in skin lesions, buccal and throat swabs, oral fluid, urine, feces, and blood samples from different stages of infection.

In addition, the lack of sewerage networks in low- and middle-income countries can limit the early-warning benefits of WBS monitoring of infectious diseases (Adhikari and Halden, 2022). If WBS samples are collected mostly from urban rivers and open sewage, there is potential for samples to be influenced by MPXV input from non-human sources. Even in resource-rich countries, when a combined sewerage system (sewage with rainwater) is practiced, MPXV can enter the sewage system from non-human sources, especially in areas closer to urban forests. Lastly, using WBS for monitoring a small population is challenging, and may pose some ethical issues and may stigmatize the sampled community that is being surveilled (Jacobs et al., 2021; Hall et al., 2012). Thus, several aspects, such as the culture and values of the community and the individuals connected to the sewer network, should be considered before disseminating the results (Polo et al., 2020; Coffman et al., 2021).

7. Conclusion

Wastewater surveillance has a progressively imperative role in developing robust surveillance systems that are a prerequisite for the efficient and timely prevention and control of both emerging and seasonal infectious diseases. Complementing clinical surveillance with WBS may help elucidate the true societal burden of the targeted infectious agent. WBS can be a valuable tool for the environmental surveillance of MPXV. In order to quickly develop and implement a robust global network of WBS for MPXV, further research is urgently needed to fill in critical knowledge gaps, such as shedding of MPXV and its DNA in feces, urine, and skin, understanding the environmental persistence of MPXV and its DNA in wastewater matrix, the infectivity of MPXV in wastewater, and analytical methods to efficiently detect MPXV DNA in the wastewater.

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CRediT authorship contribution statement

AT, TP and MAI conceptualize the manuscript. AT reviewed the literature and drafted the initial version of the manuscript together with SA, DK, and BM. All co-authors contributed and approved the submitted manuscript.

Data availability

The study has not produced any original data, and all the data used in the study are available in the manuscript.

Declaration of competing interest

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