Monkeypox Outbreak: Wastewater and Environmental Surveillance Perspective

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Review

Monkeypox outbreak: Wastewater and environmental surveillance perspective

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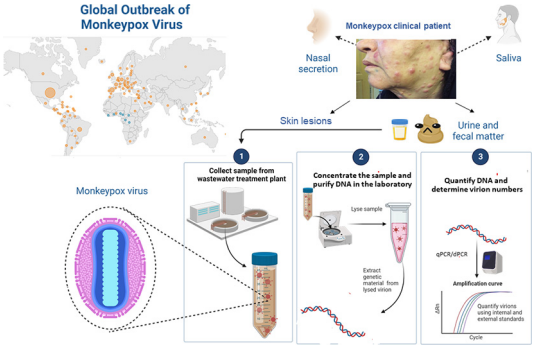
HIGHLIGHTS

- 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



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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, MPXD has been reported at least in 74 countries globally, prompting the World Health Organization to declare

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the MPXD outbreak a Public Health Emergency of International Concern. As of July 24, 2022; 92 % (68/74) of the countries with reported MPXD cases had no historical MPXD case reports. From the One Health perspective, the spread of MPXV in the environment poses a risk not only to humans but also to small mammals and may, ultimately, spread to potent novel host populations. Wastewater-based surveillance (WBS) has been extensively utilized to monitor communicable diseases, particularly during the ongoing COVID-19 pandemic. It helped in monitoring infectious disease caseloads as well as specific viral variants circulating in communities. The detection of MPXV DNA in 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, supports the possibility of using WBS as an early proxy for the detection of MPXV infections. WBS of MPXV DNA can be used to monitor MPXV activity/trends in sewerage network areas even before detecting laboratory-confirmed clinical cases within a community. However, several factors affect the detection of MPXV in wastewater including, but not limited to, routes and duration time of virus shedding by infected individuals, infection rates in the relevant affected population, environmental persistence, the processes and analytical sensitivity of the used methods. Further research is needed to identify the key factors that impact the detection of MPXV biomarkers in wastewater and improve the utility of WBS of MPXV as an early warning and monitoring tool for safeguarding human health. In this review, we shortly summarize aspects of the MPXV outbreak relevant to wastewater monitoring and discuss the challenges associated with WBS.

Contents

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, Cote 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 recently imported from Ghana (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 Furth 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 people), 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, Capripxvirus, Suipxvirus, Leporipoxvirues,* 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, uasin 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 Rodriguez-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 Rodriguez-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 MPXD

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 (Ogoina 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 MPXD 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 MPXD (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 Brincidofovir, 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 (Johnson, 2006). The WBS is a critical component of the worldwide initiative to eradicate polio outbreaks (Asghar 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; Jakariya et al., 2022; Kumar et al., 2020; Malla et al., 2022; Medema et al., 2020; Sherchan et al., 2020; Tiwari et al., 2022b). The same approach has been successfully used for monitoring many other pathogens including hepatitis E virus (Iaconelli et al., 2020), rotavirus (Santiso-Bellón et al., 2020), adenovirus (Fong 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), enterovirus (Faleye et al., 2021), canine picornaviruses (Faleye et al., 2022), dengue virus (Thakali et al., 2022), metagenome markers of many other viruses including different poxviruses from the *Poxviridae* 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 MPXD (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 MPXD.

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 MPXD-positive persons in Italy (Antinori et al., 2022). In another study in Barcelona, Spain, from 12 MPXD 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

Table 1
Comparison between clinical testing and surveillance with wastewater-based surveillance (WBS) for infectious diseases.

Clinical testing & surveillance	Wastewater-based surveillance
■ Required for confirming and treating the disease at an individual level.	■ Capability of illustrating the spatial and temporal trends and peaks of outbreaks of many communicable diseases at the community level.
■ Relatively expensive, as a clinical setting requires a lot of individual samples to have surveillance power.	■ Relatively cost-effective, as a single wastewater sample can have the whole community information.
■ Testing specimens are collected from only the symptomatic people, typically does not capture asymptomatic cases.	■ Targets all infected individuals (symptomatic, asymptomatic pre-symptomatic, and post-symptomatic cases) shedding virus particles in their excreta (nasal secretion, spit, urine, and feces) and washing water.
■ Well-established networks for transferring data and knowledge between epidemiologists and clinical laboratories. Communication mechanisms are established, and most common people understand the communicated results.	■ Interpretation and communication must be ensured by the engagement of the epidemiologists.
■ Monitoring infrastructures such as hospitals, and testing laboratories with well--trained permanent staff are available.	■ Might require building a new surveillance system, such as validation of methodology, epidemiological interpretation. WBS is emerging approach and monitoring infrastructures have not yet been fully developed.
■ Testing is voluntary and personal consent is needed for testing. Thus, testing is affected by personal willingness to be tested, and in some cases the paying ability of individuals. Sometimes social stigma may oppose clinical testing.	■ WBS is a community wide tool not affected by personal testing willingness, testing capacity, or personal consent.
■ Mostly, false negative rate is low and possible caveats of monitoring are relatively well understood	■ A low number of pathogens maybe not be enough for detecting titers in wastewater. Factors such as assay performance, PCR inhibitors, and dilution of targets in sewage systems due to precipitation can affect the assay performance and subsequently the detection rates in wastewater.
■ Cross reaction of assay can be low because most assays could be tested earlier with probable microbes from the host.	■ Cross reaction of the assay with non-targeted microbes is relatively challenging as wastewater is rich with wide varieties of environmental microbes from wide sources.
■ Relatively slow for detecting the trends of outbreaks, as data collected at individual levels need to be compiled and analyzed.	■ Mostly provides real-time disease burden at the community level.
■ Individual specific results are quite simple to interpretate.	■ Needs to be validated with clinical data. Sometimes, exact clinical data can be challenging to achieve while the disease is self-limiting, and people do not go for testing, or due to limited testing facilities.
■ Representativeness of sample, transportation conditions after sample collection and analysis errors may affect the results of any laboratory result.	■ In addition to representativeness of sample, transportation conditions after sample collection and analysis errors, also biomarker (genetic fingerprint of a human pathogen such as DNA or RNA) stability in wastewater can affect the result.
■ Result interpretation is straightforward with aim to diagnose the cause of the illness of the individual.	■ Uncertainties related to the representativeness of the wastewater sample in connection to population estimates and the content of the wastewater sample (share of human excreta)

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 MPXD as its management tool. De Jonge et al. (2022) have recently reported the qualitative detection of MPXV in wastewater influent samples in the five city districts in the Netherlands. They analyzed a total of 108 wastewater influent samples for monitoring MPXV DNA with two USCDC assays: namely, the G2R_G assay targeting the OPG002 gene (targeting all MPXV) and the G2R_WA assay targeting the OPG002 gene (targeting the West Africa clade) (Li et al., 2010), and detected MPXV DNA in 45/108 (42 %) samples (De Jonge et al., 2022). They reported that DNA extraction on the (bio) solids could yield good results (De Jonge et al., 2022). Furthermore, the detection of MPXV in 10 of 11 sewer systems in the San Francisco Bay Area (CA, USA) has been reported (Kiros, 2022; Wolfe et al., 2022b). The detection of MPXV DNA has been consisted in wastewater samples in 8 out of 9 wastewater treatment plants monitored with digital PCR in San Francisco, California, USA (Wolfe et al., 2022b). They analyzed settled solids from 287 wastewater samples and monitored MPXV with the same USCDC assays G2R_G targeting the OPG002 gene and the G2R_WA assay (Wolfe 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 10^3-times higher in solid fraction of wastewater than in liquid fraction when considered by weight/mass (Wolfe 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 sewershed communities (Wurtzer et al., 2022). They monitored a total of 264 samples collected earlier for WBS of COVID-19 with MPXV TaqMan 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 MPXD with WBS can be feasible, but the concept for MPXV monitoring is currently 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 MPXD 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 Chimpanzee (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

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations or those of the publisher, the editors, or the reviewers. RUH is a founding member of AquaVitas, LLC, an Arizona State University startup company working in the field of wastewater-based epidemiology. RUH also is the founder of the ASU non-profit project OneWaterOneHealth that is managed by the Arizona State University Foundation, and that is operating in the same intellectual space.

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