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Review

Key considerations for pathogen surveillance in wastewater

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HIGHLIGHTS

- Research is needed on shedding rates of pathogens in human feces and body fluids.
- Fate of pathogens in wastewater networks is not well-understood.
- Surveillance pipelines for each pathogen need rigorous laboratory validation.
- Varied shedding and fate of pathogens in wastewater hinder comparability.

GRAPHICAL ABSTRACT

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ABSTRACT

Wastewater surveillance (WWS) has received significant attention as a rapid, sensitive, and cost-effective tool for monitoring various pathogens in a community. WWS is employed to assess the spatial and temporal trends of diseases and identify their early appearances and reappearances, as well as to detect novel and mutated variants. However, the shedding rates of pathogens vary significantly depending on factors such as disease severity, the physiology of affected individuals, and the characteristics of pathogen. Furthermore, pathogens may exhibit differential fate and decay kinetics in the sewerage system. Variable shedding rates and decay kinetics may affect the detection of pathogens in wastewater. This may influence the interpretation of results and the conclusions of WWS studies. When selecting a pathogen for WWS, it is essential to consider it's specific characteristics. If data are not readily available, factors such as fate, decay, and shedding rates should be assessed before conducting surveillance. Alternatively, these factors can be compared to those of similar pathogens for which such data are available.

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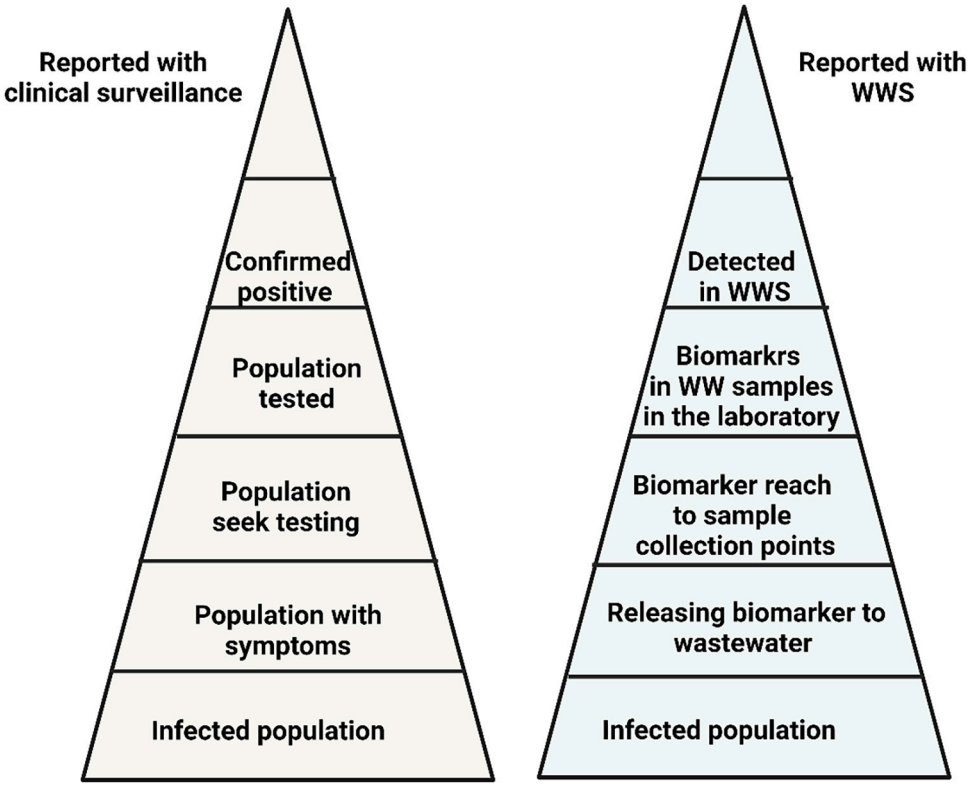

Fig. 1. A comparison of the detection and reporting of pathogens with clinical and wastewater surveillance (WW = wastewater, WWS = wastewater surveillance).

1. Introduction

Wastewater surveillance (WWS) is a powerful approach for tracking potential infectious agents and/or their genetic material cost-effectively at the population level (Ahmed et al., 2020; Fontenele et al., 2021; Kilaru et al., 2023; Sims and Kasprzyk-Hordern, 2020). It offers a promising tool to detect and assess spatial and temporal trends, as well as genetic diversity of disease-causing pathogens (Sims and Kasprzyk-Hordern, 2020). Furthermore, WWS provides data almost in real time, often days or weeks in advance of clinical manifestation (Bibby et al., 2021; Radu et al., 2022; Kumar et al., 2023; Tiwari et al., 2023). As, pathogens are introduced into the sewerage system through feces, urine, mucus, sputum, and skin from the early stages of colonization to advance infection, regardless of the development of clinical symptoms (Diemert and Yan, 2019; Tiwari et al., 2023). WWS also provides community-level results anonymously, thereby minimizing ethical challenges (Bowes et al., 2023). This approach uses noninvasive sampling, eliminating the need to collect of individual clinical specimens (Bowes et al., 2023).

Clinical surveillance is essential for individuals' targeted treatment. However, population-level clinical surveillance has limitations because not all infected individuals exhibit symptoms (Fig. 1). Furthermore, population-level clinical surveillance involves a complex process: exposure to pathogens, colonization in body tissue, manifestation of symptoms, testing, and subsequent reporting. Asymptomatic or pre-symptomatic individuals, as well as many self-limiting diseases, often remain untested clinically, leading to underreporting (Bowes et al., 2023; Mansfeldt et al., 2023). Given these limitations, integrating WWS into the existing clinical disease-surveillance framework can provide new insights into diseases' incidence, seasonal patterns, and geographical distribution (Table 1). A single aggregated 24-h composite wastewater sample taken from a catchment has the potential to provide a snapshot of various illnesses that are circulating in communities (Kuhn et al., 2023; Tiwari et al., 2024). WWS is highly adaptable, as it can be integrated into extensive networks of wastewater collection across a city. It provides flexibility in selecting targets, determining sampling

Table 1
Comparison of the advantages and limitations of wastewater surveillance.

Advantages	Limitations
Monitor spatial and temporal trends of various pathogens, variants, and antimicrobial resistance in a community.	Comparing the detection and quantification of multiple pathogens in wastewater is challenging due to variations in shedding rates, fate, and decay of these pathogens. Low abundance of pathogen(s) in wastewater does not necessarily correlate with low clinical cases in the community. This low detection rate may also be due to a low shedding rate of the pathogen.
Relatively cost-effective, as a single wastewater sample can provide information about the entire community.	Wastewater sample concentration, nucleic acid extraction, purification, and enumeration methods are not yet standardized, potentially leading to inaccurate results.
Provides real-time evidence of pathogen shedding into sewage systems, enabling early intervention by detecting pathogens before symptoms appear.	Uncertainties regarding sample representativeness, transportation conditions, and the stability of pathogens in wastewater can impact the accuracy of results.
WWS is a community-wide tool unaffected by individual testing willingness, testing capacity, or personal consent.	During the early stages of development, validating WWS with clinical data is necessary. However, obtaining such data can be challenging, especially for self-limiting diseases where testing facilities are limited.
	Detecting a low number of pathogens can be challenging due to assay performance issues, potential cross-reactions of primers with non-targeted microbes, and PCR inhibition.

frequency, and storing samples for retrospective analysis of emerging pathogens (Fochesato et al., 2021; Kumar et al., 2023; Hokajärvi et al., 2021).

While WWS is a promising tool for tracking infectious diseases at the population level, it has limitations (Fig. 1). Firstly, not all infected individuals excrete detectable levels of pathogens in wastewater, and these pathogens exhibit varying shedding rates across different modes of human excretion (Tables 1 & 2). For example, earlier studies reported SARS-CoV-2 in fecal samples at rates ranging from 30 % to 100 % (Cevik et al., 2021; Kitajima et al., 2020). Moreover, pathogens can have different fate and decay characteristics within sewerage systems, which can lead to degrading or interaction variations, thus making detection challenging (Li et al., 2023; Sharma et al., 2023; Zhang et al., 2023a). During transportation from sample collection sites to centralized laboratories, certain pathogens in wastewater samples may decay at different rates. This is due to improper transportation protocols, transportation distances, and logistical challenges among sampling sites. These factors can collectively affect the accuracy of the results (Tiwari et al., 2024). Standardizing sampling and analytical protocols and decentralizing laboratories could be a solution, but it poses challenges due to the capital investment required to establish fully equipped molecular laboratories with trained staffs. Additionally, factors such as limited resources, lack of standardized protocols, and varying surveillance practices contribute to underreporting, limiting the utility of this surveillance tool.

WWS employs various microbiological/molecular methods (e.g., culture-based, quantitative PCR [qPCR]-based, and next-generation sequencing-based methods) (Fontenele et al., 2021; Shrestha et al., 2017, 2024; Tiwari et al., 2022a). However, our understanding of the limitations and challenges of WWS remains incomplete, partly due to the wide range of pathogens and methodologies available. For accurate interpretation of data and subsequent application of results, it is crucial to consider such limitations and challenges when planning and operating WWS programs. This review discusses variations in pathogens' epidemiology, pathogenicity, shedding rates, and fate in sewer systems when using WWS for diverse public-health monitoring needs. We anticipate that the study's findings will improve the understanding and interpreting WWS for multiple pathogens.

2. Potential pathogen targets for WWS

Wastewater can be an ideal matrix for tracking pathogens from wide taxonomic ranges, including pathogenic viruses, bacteria, and microeukaryotes (e.g., protozoa and fungi) (Kilaru et al., 2023; Tiwari et al., 2024; Zhang et al., 2023b). Currently, the majority of WWS applications are related to gastrointestinal and respiratory ailments (Kilaru et al., 2023; Shrestha et al., 2024), but the practice has also been used for monitoring malaria, cholera, typhoid fever, and various arboviruses—dengue, Zika virus, and chikungunya (Chandra et al., 2021; Kinimi et al., 2018; Thakali et al., 2022; Wolfe et al., 2024). Kilaru and colleagues found that before the COVID-19 pandemic, over 25 pathogen families had been monitored through WWS (Kilaru et al., 2023). After the pandemic, WWS has expanded globally and has been piloted for or applied to various pathogens worldwide (Ahmed et al., 2023a; Boehm et al., 2023a; Radisic et al., 2023). Some commonly targeted viruses in WWS studies are summarized in Table 3.

Respiratory diseases caused by various pathogens such as respiratory syncytial virus (RSV), influenza virus, parainfluenza viruses, SARS-CoV/SARS-CoV-2, and human metapneumovirus are a global health concern. They result in illnesses such as bronchitis, sinusitis, ear infections, pneumonia, and even death (Lanrewaju et al., 2022; Noor and Maniha, 2020). However, the clinical surveillance of these viruses is compromised because these infections usually go unnoticed due to their mild symptoms and the infections frequently resolve on their own. As a result, individuals often do not seek medical attention (Boncristiani et al., 2009; Noor and Maniha, 2020).

Certain enteric viruses like HNoV, RoV, AsV, and hepatitis viruses cause gastrointestinal illnesses (Atmar et al., 2008; Cioffi et al., 2020; Lanrewaju et al., 2022; Mabasa et al., 2018; Pouillot et al., 2015; Tubatsi and Kebaabetswe, 2022; Victoria et al., 2014). Given that these viruses are shed into the sewerage system through stools, urine, and other bodily fluids in significant quantities, they hold high potential for WWS (Sims and Kasprzyk-Hordern, 2020). In addition to the viruses related to respiratory and gastrointestinal infections, other viruses—for example, those leading to hemorrhagic fever and congenital infections (Atmar et al., 2008; Boncristiani et al., 2009; Fenner et al., 1987; Lanrewaju et al., 2022; Noor and Maniha, 2020)—are a major public-health concern, particularly in low- and middle-income countries (Fenner et al., 1987; Lanrewaju et al., 2022; Noor and Maniha, 2020). Monitoring many of these viruses via wastewater can be feasible if they occur in sufficiently high numbers to be detected in the wastewater samples (Lahrich et al., 2021; Monteiro et al., 2022b; Thakali et al., 2022; Wolfe et al., 2024). Since most viruses are host-specific, their detection in sewer systems typically implies their release from humans. However, there can be exceptions; for instance, the influenza A virus can also be transmitted from zoonotic sources (Heijnen and Medema, 2011).

Bacterial infections pose a different kind of public-health concern, are also released into the sewerage system through bodily fluids. Hence, they are suitable targets for WWS as well (Doron and Gorbach, 2008; Kilaru et al., 2023; Kuhn et al., 2023; Sims and Kasprzyk-Hordern, 2020; Zhang et al., 2023c; Zhou et al., 2023). However, bacteria are less frequently targeted in this manner (Diemert and Yan, 2019; Kilaru et al., 2023; Matrajt et al., 2020; Zhou et al., 2023). Compared to viruses, they have wider host ranges and exhibit different fate and decay rates. Furthermore, in the sewer system, bacteria may exhibit high decay rates; however, they also thrive in an environment rich nutrients, which promotes their growth (Boschiroli et al., 2015; Lan Chun et al., 2015). Bacterial pathogens with a zoonotic host range, such as *Campylobacter*, *Salmonella,* and Shiga toxin-producing enterohemorrhagic *E. coli,* can be transmitted from nonhuman mammals and birds, in addition to infected human hosts (Diemert and Yan, 2019; Rahman et al., 2020). Thus, WWS targeting a zoonotic pathogen may necessitate a holistic, "One Health" approach for both result interpretation and management of the outbreak.

Table 2
Different viruses shed at varying rates in the human bodily excretion system.

Pathogenic viruses	Shedding rate (Log_{10} GC per gm or L)				Reference
	Stool	Urine	Saliva/mucus	Sputum	
Norovirus	10.98	–	–	–	(Atmar et al., 2008)
SARS-CoV-2	10.55	8.15	8.05	7.92	(Crank et al., 2022)
Rhinovirus	3.00	–		–	(Lowry et al., 2023)
Influenza	6.77	–	–	8.18	(Lowry et al., 2023)
Enterovirus	3–7	–	–	–	(Gerba et al., 2017)
Rotavirus	10	–	–	–	(Gerba et al., 2017)
Adenovirus[a]	3–10	–	–	–	(Lion, 2014)

[a] Highly varied in different serotypes.

Table 3
Viruses targeted with WWS and their detection frequency and genome copy (GC) numbers in wastewater/sludge/feces.

Target pathogen	RNA/DNA virus	Major excretion route	Infection type	Detection frequency in WW	Numbers in WW	Seasonality and vulnerable group	References
Human metapneumovirus (HMPV)	Enveloped, nonsegmented, negative-sense, single-stranded RNA virus	Cough, sneeze, spit, stools, urine, and blood	Common cold, flu-like symptoms, fever, and diarrhea, mostly in young children	–	7.6×10^2 GC/g solids WW (range: 0–2×10^3 GC/g)	Occurs year-round but may have seasonal peaks in winter	(Boehm et al., 2023a)
				100 %	9.1×10^4 to 1.6×10^7 GC/L		(Ahmed et al., 2023a)
Human bocavirus (HBoV)	Small nonenveloped virus, with linear single-stranded DNA genome	Cough, sneeze, spit, stools, urine, and blood	Common cold, flu-like symptoms, fever, and diarrhea, mostly in young children	57.5 %	6×10^3 to 4.9×10^4 GC/L	Occurs year-round but may have seasonal peaks in winter	(Hamza et al., 2017)
				79.1 %	5.51×10^3 to 1.84×10^5 GC/L		(Iaconelli et al., 2020)
Epstein–Barr virus (EBV)	Enveloped virus with an icosahedral capsid and double-stranded DNA	Saliva, blood, and other bodily fluids	Fatigue, fever, inflamed throat, swollen lymph nodes in the neck, enlarged spleen, swollen liver, and rash	89.1 %	1.2×10^4 to 2.9×10^6 GC/L	Occurs mostly in all seasons; children are more vulnerable	(Ahmed et al., 2023a)
Cytomegalovirus (CMV)	Enveloped virus with icosahedral capsid and double-stranded DNA	Saliva, urine, blood, tears, semen, and breast milk	Fever, sore throat, fatigue, and swollen glands	19.6 %	1×10^4 GC/L	Occurs mostly in all seasons; children are more vulnerable	(Ahmed et al., 2023a)
Rhinoviruses A and B (RhV A and B)	Small nonenveloped viruses containing a single-stranded RNA genome	Cough, sneeze, runny nose, spit, and stools	Most frequent cause of the common cold; mostly mild infections but sometimes can cause severe asthma	100 %	RhV A: 8.9×10^3 to 4.2×10^5 GC/L RhV B: 5.5×10^3 to 4.1×10^5 GC/L RhV A and B: 4.8×10^4 GC/g solids WW (range: 0–9.5×10^3 GC/g)	Occurs year-round but may have seasonal peaks in winter	(Ahmed et al., 2023a) (Ahmed et al., 2023a) (Boehm et al., 2023a)
Parechovirus (PeV)	Small, icosahedral, nonenveloped, single-stranded RNA virus	Cough, sneeze, spit, stools, urine, and blood	Often asymptomatic; also mild flu-like symptoms and diarrhea	100 %	1.5×10^3 to 2.1×10^5 GC/L	Throughout the year; predominantly in children globally	(Ahmed et al., 2023a; Lodder et al., 2013)
				71.7 %	1.7×10^3 to 4.1×10^5 GC/L		(Ahmed et al., 2023a)
Influenza A virus (IAV)	Enveloped, single-stranded, negative-sense, positive-strand RNA viruses	Cough, sneeze, spit, and stools	Fever, runny nose, sore throat, muscle pain, headache, coughing, fatigue, diarrhea, and vomiting	–	10^6 GC/g feces 8×10^2 to 2.7×10^6 GC/L	Often more frequent in winter; children and immunocompromised groups are more vulnerable	(Vo et al., 2023)
				–	10^3 to 3.2×10^5 GC/L 1.63×10^2 to 10^4 GC/L;		(Dumke et al., 2022)
				66.7 %; 3.8 %; 5.4 %	8.11×10 to 1.6×10^3 GC/L; 4.99×10 to 8.38×10^2 GC/L		(Ando et al., 2023)
Influenza B virus (IBV)				–	10^6 GC/g feces 8×10^2 to 2.7×10^6 GC/L		(Vo et al., 2023)
Respiratory syncytial virus A (RSV A)	Enveloped, single-stranded, negative-sense RNA viruses	Cough, sneeze, runny nose, spit, and stools	Upper to lower respiratory tract involvement, dry cough, fever, and trouble breathing in severe cases	41.3 %	1.1×10^3 to 7.1×10^4 GC/L	Often more frequent in winter; mostly all age groups but children and immunocompromised individuals are more vulnerable	(Ahmed et al., 2023a)
				Up to 72.7 %	2.11 to 10^2–5.01 to 10^3 GC/L 5.39 to 10–2.73 to 10^4 GC/L		(Ando et al., 2023)

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Table 3 (*continued*)

Target pathogen	RNA/DNA virus	Major excretion route	Infection type	Detection frequency in WW	Numbers in WW	Seasonality and vulnerable group	References
Respiratory syncytial virus B (RSV B)	Enveloped, nonsegmented, single-stranded, negative-sense RNA viruses	Cough, sneeze, runny nose, spit, and stools	Fever, runny nose, cough, sneezing, sore throat, ear pain, bronchiolitis, and pneumonia	63.0 %	5.23 to 10–3.34 to 10^3 GC/L		(Vo et al., 2023)
					1.2×10^3 to 7.6×10^5 GC/L		
					1.7×10^3 GC/g solids WW (range: 0–5.4×10^3 GC/g)		(Boehm et al., 2023a)
					1.66×10^2 to 1.52×10^3 GC/L		
				Up to 54.5 %	5.09×10 to 1.99×10^2 GC/L		(Ando et al., 2023)
Parainfluenza virus 1 (PiV 1)				8.69 %	5×10 to 2×10^3 GC/L	Often more frequent in the fall; children are more sensitive	(Ahmed et al., 2023a)
Parainfluenza virus 4 (PiV 4)				–	6.4×10^3 to 2.4×10^4 GC/L		
					3.5×10^3 GC/g solids WW (range: 1.4–6.3×10^3 GC/g)	Often more frequent in the fall and winter; children are more sensitive	(Boehm et al., 2023a)
Parainfluenza virus 2 (PiV 2)				10.7 %	$\sim 10^4$ GC/L	Often more frequent in the fall; children are more sensitive	(Ahmed et al., 2023a)
Parainfluenza virus 3 (PiV 3)				19.6 %	2.7×10^3 to 6×10^4 GC/L	Often more frequent in spring and summer; children are more sensitive	(Ahmed et al., 2023a)
SARS-CoV-2	Enveloped, positive-sense, single-stranded RNA virus	Cough, sneeze, runny nose, spit, and stools	Fever, runny nose, cough, sneezing, and sore throat	–	4.8×10^4 GC/g solids WW (range: 2.5×10^4–1.3×10^5 GC/g)	Seasonality not yet known	(Boehm et al., 2023a)
				48 % (hospital WW); 72 % (urban WW)	10^3 to 10^6 GC/L (hospital WW); 3.13 to 10^3–8.95 to 10^5 GC/L (urban WW)		(Monteiro et al., 2022a)
				30 %	10^4 GC/L		(Monteiro et al., 2022b)
Human coronaviruses (229E, OC43, NL63, and HKU-1)	Enveloped, positive-sense, single-stranded RNA virus	Cough, sneeze, runny nose, spit, and stools	Fever, runny nose, cough, sneezing, and sore throat	–	3.5×10^4 GC/g WW solids (1.7–5.6×10^4 GC/g)	Seasonal infection can be common; more frequent in autumn, winter, and spring	(Boehm et al., 2023a)
Hepatitis A virus (HAV)	Hepatitis A C and D are positive-strand, single-stranded RNA viruses, but hepatitis B is a DNA virus	Ingestion of contaminated food and water (fecal–oral route)	Fever, malaise, loss of appetite, diarrhea, nausea, abdominal discomfort, dark-colored urine, and jaundice	100 %	1.9×10^7 GC/L	No seasonality; most common in countries with poor water and hygiene conditions	(McCall et al., 2020)
				29 %	2.1×10^3 GC/L		(Cioffi et al., 2020)
				53.9 %	6.7×10 to 5.6×10^7 GC/L		(Ouardani et al., 2016)
				84 %	3×10^3 GC/L		(Beyer et al., 2020)
Hepatitis E virus (HEV)				23.2 %	6.1×10^2 to 5.8×10^5 GC/mL		(Di Profio et al., 2019)
Enterovirus (EV) group	Nonenveloped, spherical viruses with single positive-strand RNA; positive-sense, RNA viruses	Ingestion of contaminated food and water (fecal–oral route)	Fever, runny nose, cough, sneezing, and sore throat	69 %	4×10^6 to 2×10^8 GC/L	Global, mostly in the entire human gut; primarily infects young children	(Bubba et al., 2017; Pennino et al., 2018)
Rotavirus A (RoV A)	Nonenveloped, double-stranded RNA virus	Ingestion of contaminated food and water (fecal–oral route)	Severe watery diarrhea, vomiting, fever, and/or abdominal pain	84.4 %	10^3 to 10^4 GC/L	Occurs year-round but may have seasonal peaks in winter	(Tubatsi and Kebaabetswe, 2022)

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Table 3 (*continued*)

Target pathogen	RNA/DNA virus	Major excretion route	Infection type	Detection frequency in WW	Numbers in WW	Seasonality and vulnerable group	References
					3.9×10^3 to 4.3×10^7 GC/L		(Victoria et al., 2014)
Rotavirus (A–G)				55 %	1.2×10^6 GC/L		(Cioffi et al., 2020)
Rotavirus (RoV)				41.7 %	1.9×10^3 to 1.2×10^5 GC/L		(Osuolale and Okoh, 2017)
				48.9 %	10^3 to 10^4 GC/L		(Tubatsi and Kebaabetswe, 2022)
Human norovirus GI (HNoV GI)				46 %	3.2×10^5 GC/L		(Cioffi et al., 2020)
				38.5 %	10^4 to 1.6×10^6 GC/L		(Fumian et al., 2019)
Human norovirus (HNoV)				–	2.9×10^3 to 3.8×10^7 GC/L		(Victoria et al., 2014)
Human norovirus GI and GII (HNoV GI and GII)				–	1.02×10^2 to 3.41×10^6 GC/L		(Mabasa et al., 2018)
	Nonenveloped, positive-sense, single-stranded RNA virus	Ingestion of contaminated food and water (fecal–oral route)	Mostly diarrhea, vomiting, nausea, stomach pain, fever, and headache; some strains can occur with mild symptoms or be asymptomatic		10^4 to 2×10^8 GC/L with 100 % detection rate	Occurs year-round but may have seasonal peaks in winter	
				–	10^3 GC/mL		(Huang et al., 2022; McCall et al., 2020)
					6.3×10^4 GC/mL		
					5.5×10^5 GC/L		
Human norovirus GII (HNoV GII)					10^{10} GC/g stool		
				100 %	1.16×10^3 to 1.15×10^5 GC/L		(McCall et al., 2021)
				50 %	1.3×10^5 GC/L		(Cioffi et al., 2020)
				50 %	2.94×10^4 GC/L		(McCall et al., 2020)
				46.7 %	10^3 GC/L		(Tubatsi and Kebaabetswe, 2022)
					1.1×10^6 GC/L with 100 % detection rate		
Human adenovirus (HAdV)	Nonenveloped, icosahedral virus with linear, nonsegmented, double-stranded DNA	Cough, sneeze, spit, and stools	Flu-like symptoms, fever, sore throat, acute bronchitis, pink eye, acute gastroenteritis; most people have mild or no symptoms	–	3.1×10^5 GC/L with 100 % detection rate	Global, but more frequent in regions with poor sanitation (e.g., developing countries)	(Fong et al., 2010; McCall et al., 2020)
					2×10^5 to 6.3×10^8 GC/L with 54 % detection rate		
				100 %	$6 \times 10^7 \pm 15$ GC/100 mL		(Verani et al., 2019)
				–	5.4×10^6 GC/L		(Cioffi et al., 2020)
					1.1×10^5 to 4.6×10^6 GC/L (average: 1.4×10^6 GC/L)		
Sapovirus	Nonenveloped, positive-sense, single-stranded RNA virus	Ingestion of contaminated water (fecal–oral route)	Diarrhea, vomiting, nausea, stomach pain, fever, and headache, but some strains can occur with mild symptoms or be asymptomatic	94.4 %		Occurs year-round but may have seasonal peaks in winter	(McCall et al., 2021)
				94 %	1.36×10^6 GC/L		(McCall et al., 2020)
Sapovirus (GI, GII, GIV, and GV)				57 %	1×10^6 GC/L		(Cioffi et al., 2020)
					3.2×10^3 to 4.3×10^7 GC/L		
Astrovirus (AsV)	Nonsegmented, single-stranded, positive-sense, nonenveloped, RNA virus	Ingestion of contaminated water (fecal–oral route)	Diarrhea, vomiting, fever, and/or abdominal pain	45 %		High prevalence in the cold season	(Victoria et al., 2014)
				74 %	1.7×10^7 GC/L (sludge); 7.4		(Cioffi et al., 2020)

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Table 3 (*continued*)

Target pathogen	RNA/DNA virus	Major excretion route	Infection type	Detection frequency in WW	Numbers in WW	Seasonality and vulnerable group	References
Human polyomavirus (HPyV)	Nonenveloped, double-stranded DNA virus with a circular genome	Respiratory and fecal–oral route	Respiratory illness	72.7 %	$\times 10^6$ GC/L (influent) 2.79×10^5 GC/L 2.56×10^5 GC/mL	No seasonality (occurs year-round)	(Hamza and Hamza, 2018) (Hughes et al., 2017)
Human papillomavirus (HPV)	Small, nonenveloped DNA virus	Sexually transmitted disease, skin-to-skin touching	Mostly asymptomatic but can cause lumps around genital organs	30.5 %	1.68×10^3 GC/L	No seasonality (occurs year-round)	(Hamza and Hamza, 2018)
Aichivirus (A–C) (AiV A-C)	Nonenveloped, positive sense single-stranded RNA virus	Gastroenteritis	Diarrhea, vomiting, fever, and abdominal pain	40 %	3.4×10^6 GC/L	No seasonality (occurs year-round)	(Cioffi et al., 2020)

Concerning antibiotic-resistant bacteria (ARB), members of the *Enterobacteriaceae* family, including strains producing extended-spectrum beta-lactamase and carbapenemase-producing *Enterobacterales* strains, pose global health challenges due to their resistance and impact on patient outcomes (Blaak et al., 2021; Fladberg et al., 2017; Radisic et al., 2023). Many ARB may circulate in the population without individuals experiencing clinical symptoms. Certain carriers can even transmit infections during the incubation period (Doron and Gorbach, 2008). WWS may offer advantages in determining the spatial and temporal diversity of ARB and the related genes and in identifying their potential reservoirs and sources for expanding bacterial-species surveillance (Hutinel et al., 2019; Karkman et al., 2020; Pärnänen et al., 2019).

2.1. Considerations for pathogen selection

Several factors need to be considered prior to the selection of particular target(s) for WWS in order to effectively and efficiently utilize the limited resources available. These factors are (a) epidemiological relevance and public health significance, (b) microbiological evidence, and (c) practical feasibility (Gentry et al., 2023; Tiwari et al., 2024). A pathogen selected for WWS should be epidemiologically significant enough to warrant a public-health response. The adoption of WWS is justified when pathogens can be detected early in wastewater supplementing clinical testing. This method enables health authorities to gain insights into pathogen circulation within communities, aiding to identify emerging threats and facilitate effective management. It informs decision on resource-allocation and guides intervention prioritization, including vaccination campaigns and public communication strategies. WWS can also benefit the public by promoting awareness and precautionary measures against pathogen outbreaks. Furthermore, it can assist medicine and vaccine developers in directing their efforts toward the correct pathogen strains (Tiwari et al., 2024).

Microbiological evidence is the next important factor determining the selection of pathogens. An ideal pathogen and it's genetic fragments must be present in wastewater at high concentrations to be reliably detected through sampling and analytical techniques (Capone et al., 2020; Gentry et al., 2023). Moreover, evidence of consistent shedding from infected hosts into the sewage system is crucial for establishing a reliable pathway for pathogen dissemination in wastewater (Table 2). It is essential to recognize that the shedding rate of pathogens into wastewater may vary depending on factors such as pathogenicity, infection rate, and seasonality (Table 2). These factors offer insights into disease dynamics and transmission patterns, with seasonal changes potentially reflecting shifts in human behavior, environmental conditions, or disease prevalence.

Practical feasibility is also an important consideration when selecting pathogens for WWS. Sufficient human and laboratory resources, including specific molecular assays, well-designed oligonucleotides, and sequencing facilities, are needed for effective WWS of pathogens (Pruden et al., 2021). A specific and sensitive analytical method must be readily available for the chosen pathogen, or it must be developed (Gentry et al., 2023).

The consideration and selection of targets are influenced by the availability and choice of monitoring methods. For instance, the resources needed for culture-based and qPCR-based methods increase as the number of targets expands. However, with high-throughput tools such as metagenomics and high-throughput qPCR-based methods, the demand for additional resources may not significantly increase when incorporating new pathogens of interest.

3. Complexities in WWS

WWS entails limitations and uncertainties (Figures 1, 2 and Table 1), that need to be carefully considered (Michelle and Melissa, 2023; Wade et al., 2022).

- **Population-related factors,** such as vaccination and prior infection rates, may influence individual shedding rates, the duration of shedding, the pathogen's profile, and disease-transmission dynamics (Michelle and Melissa, 2023).
- **Wastewater network-related factors,** such as uncertainties in target decay (temperature, redox conditions, residence time in the sewer, and biocidal chemicals), industrial-effluent dilution, precipitation, and groundwater infiltration, may affect target detection, especially quantification in wastewater (Li et al., 2023; Zhang et al., 2023a).
- **Sampling and storage considerations** involve sampling type (i.e., grab vs. composite), sampling time and duration, sampling location and frequency, transportation of sample, and storage of samples (Tiwari et al., 2023).
- **Analysis-related uncertainties** encompass factors such as the recovery efficiency of sample concentration and extraction methods, sample detection and quantification limits, the number of technical and biological replicates, the preparation of accurate standard curves for qPCR/RT-qPCR, PCR inhibition assessment, and data interpretation (Ahmed et al., 2022).

Addressing the above uncertainties is crucial for making informed decisions for public health. If WWS is deemed important, it becomes necessary to establish surveillance tools through collaborative efforts. This requires building capacity, training personnel, empowering institutions, and establishing communication channels (Fig. 2).

3.1. Challenges arise in interpreting clinical cases compared to WWS data

One approach to validate the accuracy of WWS is to establish a clear connection between wastewater data and clinical cases within specific

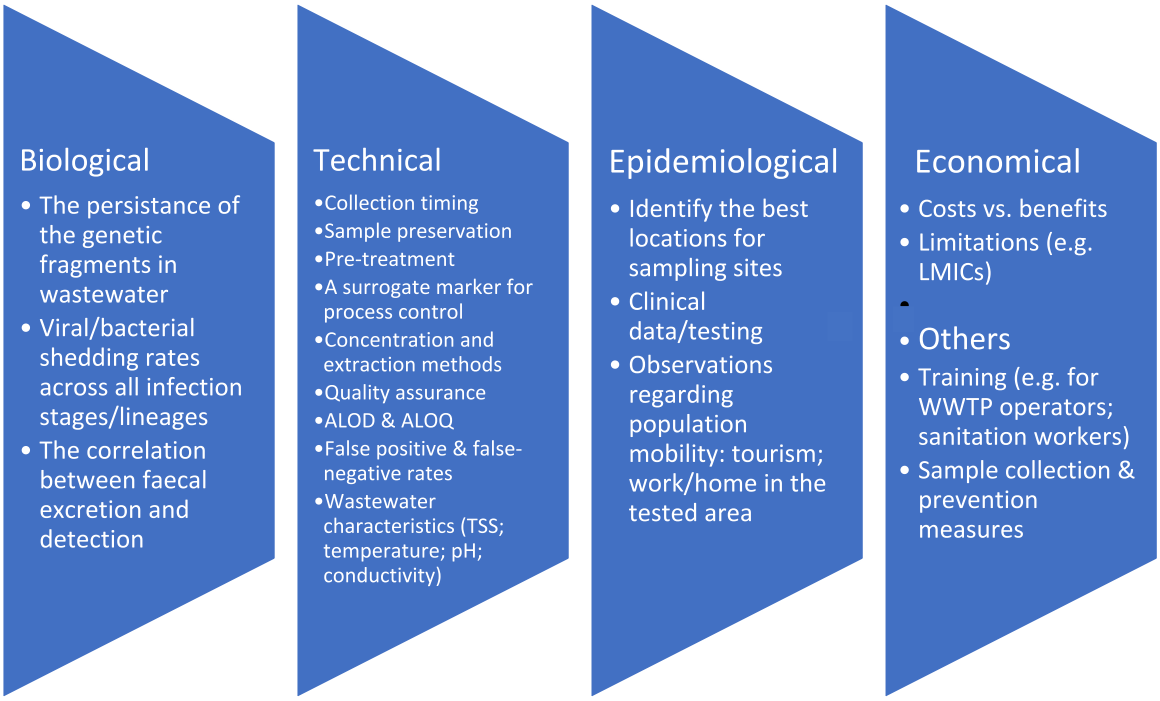

Fig. 2. Complexities in WWS, summarized based on key criteria. ALOD = analytical limit of detection; ALOQ = analytical limit of quantification; LMIC = low- and middle-income countries; WWTP = wastewater treatment plant.

sewersheds. This facilitates communication with epidemiologists and health authorities to better understand the value represented by WWS as a novel public-health monitoring tool. However, numerous factors influence establishing the connection between clinical cases and WWS.

a. **Variation in population size and dilution of pathogens in sewerage systems**

Population sizes vary across different catchments due to factors such as urbanization and mobility. Furthermore, pathogens in sewerage systems can be diluted by precipitation, industrial discharge, and variations in per capita water consumption. These factors can vary in the same catchment over time, influencing the degree of sewage dilution and thereby affecting the concentration of pathogens in wastewater. This variability may impact the accuracy of their quantification (Arts et al., 2023; Ji et al., 2021). To address these challenges, various pathogen-data normalization methods, including flow-population normalization and the use of microbial or chemical indicators, have been applied (Arts et al., 2023; Li et al., 2021; Maal-Bared et al., 2023).

Dilution can result in pathogen numbers drop below the assay detection limit, potentially affecting the detection rate, especially when pathogens are present in wastewater at low concentrations. Hence, effective concentration/extraction methods and sensitive quantification techniques should be used for low-level pathogen detection/quantification (Ahmed et al., 2022). When dealing with low concentration of pathogens, digital PCR (dPCR) has been found to exhibit higher sensitivity compared to the qPCR platform for the analysis of various microbes (Tiwari et al., 2022b).

b. **Variation in shedding rates**

Establishing a relationship between wastewater pathogen data and the corresponding clinical cases within a sewershed can be complex. This complexity may be due to the variable shedding rates of pathogens by infected individuals (Cordey et al., 2017; Prasek et al., 2023). Crank and colleagues estimated that infected individuals contribute about 8.05 $\log_{10}$ SARS-CoV-2 gene copies (GC) via saliva, 7.92 $\log_{10}$ GC via sputum, 8.15 $\log_{10}$ GC via urine, and 10.55 $\log_{10}$ GC via stool per day (Crank et al., 2022). An infected individual may not shed SARS-CoV-2 via all these sources, but if they do, the SARS-CoV-2 GC numbers in wastewater will be increased significantly (Crank et al., 2022).

Shedding rates can also vary among different strains or lineages of pathogens (Table 2), among various clinical groups (including children, adults, the elderly, males, and females), and across distinct stages of infection (Lowry et al., 2023). Each pathogen has its unique sources, shedding and decay rates, pathogenicity, and symptoms. Potential fluctuations in shedding rates can impact the presence of a pathogen in wastewater, leading to difficulties in linking WWS outcomes to clinical data. For example, metagenomics and high-throughput qPCR are powerful detection tools for simultaneously monitoring multiple targets; hence, they offer a comprehensive view of microbial community. However, these tools do not account for variations in the shedding rates of the monitored pathogens (Karkman et al., 2020; Liguori et al., 2022; Waseem et al., 2019). Thus, the absence of pathogens in a wastewater sample does not indicate the absence of infected individuals in the sewershed. Some targets may have low shedding rates and faster decay, which further complicates interpretation. Unfortunately, shedding information is unavailable for many pathogens, indicating the need for cautious data analysis and intepretation.

c. **The lack of clinical testing and different reporting systems**

Many infection types lack documented shedding-rate information, largely because current clinical laboratories mainly utilize a binary reporting system (infected/not infected) (Lowry et al., 2023). Similarly, there is often a lack of data on shedding rates for antimicrobial-resistant pathogens as well as their various strains and genes in clinical cases (Blaak et al., 2021; Tiwari et al., 2022c). Increasing collaboration between epidemiologists, clinical laboratories in health-care systems, and researchers may overcome these limitations in the future. The shedding rate of each pathogen in wastewater represents the key factor in understanding and modeling the pathogen's occurrence, dissemination, and impact on public health (Li et al., 2021). The availability of shedding-rate information from clinical patients has an important role in

perfecting WWS for COVID-19, supporting the reliable mathematical modeling of SARS-CoV-2 RNA in wastewater. Such shedding rate information helps for establishing a relationship between WWS data and clinical surveillance data, and demonstrating that WWS can accurately capture trends and peaks of COVID-19 cases at the local and national levels (Bibby et al., 2021; Lastra et al., 2022). However, for many diseases (mainly self-limiting ones), the clinical data in question can be highly underestimated due to low clinical testing (Boehm et al., 2023a, 2023b). Often-asymptomatic, self-limiting, and mildly symptomatic infections can have low testing rates (Lowry et al., 2023).

d. **The source, fate, and decay of pathogens in the sewerage system**

Bacterial pathogens and protozoan parasites typically have a wide range of hosts and can also originate from zoonotic sources. Human and zoonotic pathogens predominantly thrive in areas of the body where temperatures are within the mesophilic range (~37 °C), environments with high nutrients and salt, anoxic conditions, and locations with high osmotic pressure in the gut (Hu et al., 2014; McLellan and Eren, 2014; Newton et al., 2015). When pathogens are released into an external environment, they face various ecological pressures. The fate and survival rates of microbes across taxonomic groups in the sewer network will vary due to exposure to various physical and chemical stressors (McLellan and Eren, 2014).

This challenge is notable when monitoring ARB and antibiotic resistance genes (ARGs) in wastewater to establish their relationships with clinical data at the population level. This is due to the following factors: (a) mobile genetic elements (MGEs) carry resistant genes that ARB pick up in the sewerage system; (b) ARB can share MGEs with environmental bacteria and vice versa; (c) pathogens can arise from asymptomatic carriers and animal sources (companion animals and livestock); (d) bacteria carrying ARGs can be part of normal human microbiota and are not accounted for in clinical testing; and (e) many ARB may be released sporadically, which means that they may not be detected frequently in wastewater samples (Pruden et al., 2021; Tiwari et al., 2022c). Therefore, interpreting WWS results for ARB/ARGs can be complex compared to host-specific viruses (Tiwari et al., 2022d). Like zoonotic pathogens, ARB and ARGs may need a comprehensive "One Health" approach to the interpretation of results and the adoption of a holistic management strategy (Tiwari et al., 2022c).

3.2. The need for standardized monitoring protocols

As WWS has only recently been introduced for many pathogens in surveillance schemes, standardized protocols are still lacking. Laboratory protocols should demonstrate high sensitivity, specificity, reproducibility, and broad applicability to facilitate WWS. However, diverse approaches are being currently used for monitoring, especially regarding pathogen concentration, nucleic acid extraction, and detection/quantification. Since different pathogens have different morphologies, physiologies, and genomic characteristics (Chahal et al., 2016; Doron and Gorbach, 2008), a method that proved effective for one pathogen may not be equally effective for other pathogens (Ahmed et al., 2023b, 2023c).

The choice of monitoring methodology is affected by the purpose of surveillance. For example, targeted approaches (PCR-based and amplicon-sequencing approaches) can be useful for monitoring known pathogens of concern (Tiwari et al., 2023), and untargeted metagenomics and metatranscriptomic shotgun-sequencing approaches can be helpful for broad population-level screening (Tiwari et al., 2023). This makes WWS an important tool for detecting new and emerging pathogens and providing early warnings at the population level. Every method has advantages and disadvantages; thus, multiple methods (e.g., culturing, qPCR, and metagenomics) can be employed if required.

3.3. The governance of WWS programs

Challenges in WWS often stem from inadequate funding and unclear guidance concerning the selection of pathogens, frequency of sampling, coverage of monitoring programs, and research and development (R&D) approaches. However, globally, some notable efforts are heading toward the institutionalization of WWS, such as the ongoing revision of the Urban Wastewater Treatment Directive of the European Union (EU). This revision would entail the regular monitoring of influents and effluents in urban wastewater systems, which would address some of the concerns above (EU Regulation 2020/741, 2022). Based on the proposed revisions, EU member countries would have to set up national systems of cooperation and coordination between health authorities and wastewater treatment plant (WWTP) operators. The aim of these systems would be to identify emerging pathogens, such as novel SARS-CoV-2 variants, poliovirus, influenza virus, and other viruses that can potentially be monitored at the influents of WWTPs (EU Regulation 2020/741, 2022). Member countries would have to determine locations and frequencies for urban wastewater sampling and analysis based on subjective evaluations, such as available health data, public-health needs, and local epidemiological conditions. Establishing an effective WWS system for both routine monitoring and pandemic preparedness will significantly add to the surveillance toolbox used to detect and control communicable diseases. This types of regulatory requirements of monitoring various pathogens generate long-term wastewater data. Using machine learning and artificial intelligence, analyzing long-term wastewater data alongside clinical reports could significantly improve the predictability and usability of WWS in coming years.

4. Conclusions

- The usefulness of WWS for many pathogens is currently poorly understood. Strengthening its role will require conducting detailed studies on shedding rates and pathogen persistence (including the persistence of genetic material) as well as developing rapid and inexpensive analytical methods. Further research is needed to establish appropriate normalization procedures that can account for sewage flow and industrial discharges. These will facilitate the sharing and comparison of findings across different time frames and geographic areas.
- The complexity of WWS stems from pathogens originating not only from symptomatic individuals but also from asymptomatic carriers and animal sources. Evaluating each pathogen's performance separately in the sewerage system in terms of occurrence, fate, and decay is crucial for advancing WWS and establishing it as a reliable surveillance tool. These are important goals given that WWS can measure ongoing outbreaks, serve as an early warning system, and assess the risks associated with various pathogens.
- The data on each pathogen might require different interpretations due to variable clinical loads, different fate and decay rates in the sewage system, and distinct opportunities and limitations. Therefore, future studies of the occurrence of individual pathogens in the sewerage system and methodological developments must employ careful, case-specific approaches.

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CRediT authorship contribution statement

Ananda Tiwari: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Elena Radu:** Writing

– original draft, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Norbert Kreuzinger:** Writing – review & editing, Supervision, Resources, Project administration, Investigation. **Warish Ahmed:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis. **Tarja Pitkänen:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Project administration, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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