

# Wastewater-based epidemiology for surveillance of infectious diseases in healthcare settings

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## Abstract:

Purpose of review:

Wastewater-based surveillance (WBS) (epidemiology) using near source sampling (NSS) in large buildings, hospitals and care homes is reviewed covering three main areas i) state of the art wastewater-based surveillance, ii) benefits / opportunities NSS has for hospital infection control systems and iii) new insights from hospital wastewater surveillance and policy implications.

Recent findings:

Wastewater provides aggregate, anonymous sources of data where the spatial resolution can be linked to populations being served. In hospitals, clear links established between wastewater RNA-fragments signal to nosocomial COVID-19 cases/outbreaks. Detecting other targets from hospital wastewater such as antimicrobial resistance markers is considered a substantial opportunity for this technology. Other clinically relevant infections i.e., influenza and monkeypox can be perceived, and sub-variant resolution to target public health response in near real time to benefit hospital infection control. WBS can reduce hospitals' clinical testing requirements as diagnostic costs are aggregated into fewer samples while still detecting single cases.

Summary:

WBS using NSS can inform infectious disease monitoring earlier, faster, and cheaper than conventional monitoring. Routine sampling using wastewater provides a platform for risk-based sampling and enables smarter allocation of resources. Finally, hospital wastewater can be used for the benefit of the wastewater surveillance field as a promising source to monitor emerging threats and resolve longstanding questions on faecal shedding. Hospital monitoring in low-income settings is considered a priority for future research.

Keywords: COVID-19, SARS-CoV-2, Wastewater-based epidemiology; Infectious diseases; Hospital, Risk management, Public Health.

## Introduction

Emerging or re-emerging infectious disease-causing agents of anthroponotic origin kill or injure millions of people annually and represent a persistent and evolving global health threat(1). Proximity of human and livestock populations and proximity to wild animal pathogen reservoirs facilitate zoonotic spill-over; this increases both frequency and potency of novel human pathogen interactions(2) and drives the (re)emergence and transmission of communicable diseases(3). Against this backdrop, public health surveillance is vital for risk assessment and risk reduction of disease impacts through implementation of effective management frameworks(4). Enhanced forms of surveillance are vital for diseases which transmit at similar levels irrespective of whether contagious individuals are asymptomatic, pauci-symptomatic, pre-symptomatic or symptomatic as evident for COVID-19 disease (SARS-CoV-2). In the case of COVID-19, new forms of monitoring were essential, as conventional public health clinical and outbreak measures rely on detecting and treating symptoms(5) or screening (e.g., exposure, routine screening for health care workers)(6) which remain inadequate to mitigate onward transmission.

One growing atypical approach for infectious disease monitoring is wastewater-based surveillance (WBS), alias wastewater-based epidemiology(7). Wastewater is an aggregate from various water sources including municipal, industrial and stormwater. This amalgam is derived from 'upstream' population and includes fomites within a complex matrix derived from faeces, urine, sputum, blood and vomit, obtained from toilets, sinks and showers which can be interrogated for population health assessment purposes(8). The value of WBS is part derived from the notion that ineffective clinical testing coverage was leading to an underestimation of community disease burden. Wastewater surveillance works as agents derived from infected individuals such as the virus, bacteria or other parasites are shed into this stream and data is unbiased with respect to individuals' health seeking behaviour. In addition, it is anonymous as it is not readily traceable to individuals or groups and therefore is ethically acceptable for large populations(9). Wastewater-based surveillance schemes have shown value for tracing poliovirus outbreaks, chemical markers of human populations and illicit

drug use in catchments (Figure 1). Since then, WBS was expanded for monitoring of many other enteric viral diseases including norovirus, adenovirus, hepatitis A and E viruses, and the non-enteric viruses including papillomavirus, polyomavirus, monkeypox and influenza(7,10–12). With respect to SARS-CoV-2, early studies during the COVID-19 pandemic suggested that the virus' genetic material shed in faecal material (13), remains in wastewater(14), is non-infectious in water medium(15) and reflects to some degree the community infection burden(16).

Formal relationships between SARS-CoV-2 RNA in wastewater and associated COVID-19 clinical case data emerged(17) although substantial variability was evident between populations, demographics and types of wastewaters, which compounded early WBS efforts and challenged scientists and public health practitioners to develop new ways to handle these 'non-standard' data streams (18). One key challenge was lack of clear consensus on strategies to normalise viral concentrations being generated to wastewater flow and loads scaled by population(18,19). Subsequent studies highlighted SARS-CoV-2 virus titres reflected infection levels / positivity rates in catchments and empowered forecasts of local and regional infection dynamics(20). High throughput screening and rigorous analysis enabled great strides to reduce authorities' large scale clinical testing requirements by providing robust, rapid and inexpensive estimates of community infections(21). Overall, consensus was that WBS should be applied as a complementary tool to aid clinical testing for infectious diseases or as part of a formal framework for infection monitoring where conventional tools are lacking (i.e., reagent / testing kit shortage) or for hard-to-test or especially vulnerable populations(22). Within this context, centralised facilities such as wastewater treatment plants (WWTP) served as aggregate, sources of anonymous data where the spatial resolution was linked to populations being served – which was useful in countries with highly centralised facilities(19). However, this was a major limitation of the approach for resource constrained countries, situations without established wastewater conveyance networks or where open defaecation is practised(23,24). Three other limitations of traditional WBS emerged: firstly, other sources i.e., combined sewers have dilution from runoff and industrial effluents thus variability in composition and quality of wastewater impacted the signal which could be recovered

from COVID-19 infected individuals, who were shedding in the sewer catchment(25). Secondly, it was difficult to gain specific information about infections linked to populations of interest (e.g., high risk groups) especially as individuals' transit between sewersheds (26) and finally, convalescent individuals shed substantial load of virus in faeces during period of recovery and substantially longer than their period of peak infectivity, effectively reducing sensitivity to detect new outbreaks under high transmission scenarios(27,28)

## Near Source Wastewater-based Surveillance for Infectious Disease Monitoring

To overcome these limitations, alternative approaches were pioneered involving near-source sampling (NSS), which involved the collection of wastewaters within the sewage conveyance system or storage network upstream of treatment plants including nodes or storage points(29). Surveillance schemes have been undertaken from local level such as room, dormitory, building wing, and single dwellings(30). This was expanded to congregate settings including large buildings or institutions (e.g., university campus)(31). For example, samples have been obtained from conveyance points, clusters of buildings and high-risk closed spaces with dense populations including industrial settings e.g., meat processing facilities(32), transport systems including aircrafts(33) and ships(34) which contain highly mobile transient populations which act as seeds for onward disease transmission. The NSS technology was coupled with clinical testing at the University of Arizona to monitor COVID-19 infections in near real time which was i) important to aid containment of infected individuals and so arrest a potential outbreak and ii) aid in calibration efforts to apportion faecal shedding to numbers of infected individuals(35). Therefore, NSS is sensitive for identifying acutely occurring incident cases in tightly defined populations i.e., persons with similar ranges of disease susceptibility. For example, NSS has been applied in high risk congregate environments stratified socially (age, gender, religion, health or social determinants) including schools(36), prisons(37), athlete accommodation(38) immigration / quarantine / isolation facilities(39), hospitals(40–45) and assisted living facilities(46). The focus of the remainder of this review will be on application of WBS for monitoring novel and re-emerging infectious

disease threats in hospitals and assisted living facilities (care homes) as congregate settings of high transmission potential with extremely susceptible populations.

## Why could hospitals benefit from wastewater surveillance?

Infectious diseases outbreaks represent existential threats to congregate communities, especially patients in hospitals(47), as inhabitants have several risk factors; many are elderly, immunocompromised or infirm with additional co-morbidities which can lead to negative prognosis(47). Overcrowding of wards and emergency departments compounds this issue during community outbreaks, which results in proximity between infected and non-infected individuals (48) and for COVID-19 this attributed a disproportionate burden of nosocomial infections and fatalities of diseases to elderly within hospital(49) and residential care(50,51). Intensive cross-sectional or admission diagnostic testing may be sufficient exercise for control of most infectious diseases within hospitals. However accurate recognition of (a)symptomatic inpatient is a prerequisite for whole system control of COVID-19 as an example(52). This is also important during discharge of patients into the community, as hospitals including other healthcare settings such as long-term care facilities have the potential to drive disease dynamics through amplification of and transmission into surrounding communities(53). Despite improved infection prevention and control measures, healthcare facility associated outbreaks of COVID-19 are increasingly being reported(54). However, it is evident from the COVID-19 pandemic that new approaches to surveillance are required to help protect hospitalized patients and healthcare professionals.

When compared to monitoring in a region or community, hospitals and healthcare facilities can benefit from and utilize information gathered from monitoring for pathogens of concern. Strategies such as isolation of cases within dedicated facilities, social distancing measures, implementation of personal protective equipment or mask mandates, elevated hygienic control measures and readily accessible data for contact tracing (i.e., next of kin, visitor records etc) are available to curb infections – options not routinely available within most communities where WBS is practised (Figure 1). To

realise the benefits of NSS in hospital / care settings it is first essential to consider limitations within the context of these applications of the WBS technology. First, dearth of data on virus faecal shedding by infected individuals and how variants impact faecal shedding load makes it difficult to attribute the pathogen loading directly to case numbers(35,55). This is confounded by lack of data on impact of vaccines to faecal shedding rates and ability of variants to evade immune response (37). Second, determining the scope of the contributing population (e.g., defecation frequency and variable numbers of transient hospital populations); and third, interference from other water sources, such as industrial scale laundries and onsite catering facilities, diluting or degrading marker signals of infectious disease(56).

## New insights from hospital, healthcare facility and healthcare system wastewater surveillance and policy implications

Hospital-associated outbreaks of infectious diseases such as drug-resistant pathogens and viruses are increasingly being reported(57). For many diseases nosocomial cases have worse prognosis compared to those with community-acquired disease, experiencing longer hospital stays and increased mortality which tends to derive from other co-morbidity / risk factor (58). Wastewater surveillance has been undertaken to monitor hospital infections of COVID-19 in numerous countries including Thailand, Canada, South Africa, Brazil, USA, China and Slovenia(40,41,44,59–63). From these data many researchers have tried to gain insights to resolve faecal shedding in populations sampled via conventional and NSS (64–66). Hospitals present a unique opportunity to undertake this strategy as patients often provide faecal samples used for typing other pathogens. In addition, clinical nasal swab tests are performed regularly for infection control purposes, providing an opportunity to triangulate cases to faecal shed load with downstream wastewater concentrations. This triangulation would only be possible through controlled trials in clinics and other settings. Sometimes, clinical anal swabs are administered to patients within hospitals / care homes, for routine screening and or diagnostic testing and these samples could also be used in place of faecal samples(67,68) For example, in patients with SARS-CoV-2 infection, throat and anal swabs did not differ significantly and correlated well (84%) in

both the paediatric and adults(68). In addition, social and demographic data alongside detailed medical records within hospitals would facilitate additional epidemiologic correlations and could enable more insights into factors contributing to severe disease (Figure 1). As patients represent a vulnerable and non-anonymous population, consent is often a pre-requisite and a strict ethical code is required for research with approval from an ethical review board(37) and their appropriate clinical care team. Providing patients data are protected and anonymised (where possible) during WBS studies and compliance achieved to the local data protection rules, then correlations between wastewater and patient data should yield practical insights to protect patient health not available to studies in community. This could include social determinants of infection risk / severity such as working patterns, social mixing, or household income(69–71). Targeted interventions such as telephone medical appointments, enhanced cleaning and contact tracing in hospitals and care homes can then be realised to break chains for nosocomial and indirect community transmission (Figure 1). An excellent example of the approach was a study from Ma et al. (72), that utilised these newborn blood to determine maternal SARS-CoV-2 antibody prevalence with regional wastewater samples used for surveillance to determine COVID-19 trends which was particularly useful in settings where diagnostic testing is limited. Using data, they retrospectively linked cumulative case burden using antigen test to assess seropositivity in a difficult to vaccinate and non-test populations (i.e., pregnant women) to COVID-19. A substantial fraction (98-99%) of the Massachusetts, (US) population was susceptible from November 2019 to December 2020. They noted prevalence increased following sustained periods of SARS-CoV-2 community transmission linked to emergence of a new variant, showing the applicability of these hospital acquired datasets and use alongside wastewater data.

In addition to using other samples / data, WBS using NSS has itself been used to measure other targets from hospital wastewater. Eze et al.(59) used NSS of hospital wastewater and isolated a pan drug resistant *Acinetobacter baumannii* strain responsible for nosocomial infections and fatalities. Hospital wastewater has value for understanding impact of hospital on driving antimicrobial resistance, especially as emerging tools such as metagenomics, target enrichment, lab-on-chip style, sample prep

automation approaches become more mainstream, providing a flexible platform for NSS monitoring to study infections within congregate communities. Spurbeck et al.(73) was able to detect numerous bacteria, fungi and virus within WBS samples via NSS using qPCR, targeted sequencing, and total RNA sequencing. Vo et al. (74) designed a community-scale wastewater monitoring program to detect influenza viruses in municipal WBS and NSS at elementary schools. The authors found vaccine-resistant influenza strains within this vulnerable subpopulation. Sequencing revealed they belonged to the 2a.2 subgroup of the influenza A (H3N2) subclade 3C.2a1b.2a and its emergence coincided with a period of poor vaccine coverage alongside deregulation of social distance and mask mandates. School wastewater was positive at 3 of the 6 schools studied peaking at  $2.7 \times 10^6$  gene copies per litre in one school, while at the WWTP it was not detectable at any point in the study. This study validates for another respiratory pathogen that building level WBS provides more spatial granularity than WWTP level(75). Wastewater surveillance has also been shown useful for notifying building occupants following a positive wastewater sample. In schools and other settings this notification significantly associated with increased diagnostic testing uptake(75,76). As hospitals are also areas for enhanced respiratory transmission, this suggests wastewater could be one approach to proactively monitor vulnerable communities and elicit behaviour change better during periods of enhanced risk. This is useful as shown on a study by Boehm et al. (77), who used RT-qPCR to track in near real-time SARS-CoV-2 sub-lineage circulation. It was suggested that targeted prescriptions could be made based on regional dynamics of variants-based appropriateness of different drugs to different populations, based on knowledge of the dominant sub-variant circulating from a spatial and temporal perspective. Acosta et al. (40) sampled 3 hospitals using NSS and assayed for conventional markers of SARS-CoV-2 in wastewater using RT-qPCR, normalising the SARS-CoV-2 loading to faecal virus biomarker Pepper mild mottle virus (PMMoV). The detectable SARS-CoV-2 virus increased in concordance with the number of hospitalisations. The study highlights that apparent nosocomial infections and specific outbreaks attributed to departments within hospitals were detectable via an increase in the wastewater SARS-CoV-2 signal above baseline. Extrapolating from this, hospital-based wastewater data suggested that

peak faecal viral shedding may occur prior to or synchronous to symptom onset. The justification provided by authors was that the congruence of wastewater RNA-signal and nosocomial cases and outbreaks that occurred within hospitals was facilitated by the short transit time provided by the NSS locations with minimal opportunity for dilution(8)decay of virus signal(78) or interaction with the biofilm on sewer surfaces (79). The authors conclude that WBS using NSS of SARS-CoV-2 represented a significant and positive tool for SARS-CoV-2 passive surveillance and for pertinent in hospitals was potential for case identification, containment(35) and mitigation in acute- care medical facilities(40).

To translate WBS data into practical clinical outcomes and provide a sustainable future for WBS, the technology needs to be integrated within existing frameworks for disease surveillance. Berry et al. (6) suggested tiered surveillance approach for infectious disease monitoring involving i) WBS, ii) representative population-based testing (alongside social determinants of health such as race, income etc) and iii) genomics to efficiently monitor disease trends and spot new variants. Overall, this would enable decision makers to prioritise investment and resource allocation during periods of low disease incidence and rapidly deploy resource to prevent outbreaks and onward disease transmission. Petros et al.(69) showed the value of collecting social data including Wi-Fi colocation information from university students alongside NSS using wastewater. The authors showed that length and frequency of social interactions alongside participating in high-contact sports were good predictors of COVID-19 infection risk. This study has interesting implications for hospital patients who are likely to be exposed to similar activities of heightened transmission risk (i.e., operations, sanitary cleaning etc), potential poor personal hygiene practise in clinic and greater numbers of social interactions than majority of adult population (from healthcare workers, visitors, physicians, carers etc).

## Conclusions, Limitations and Future perspectives

Wastewater surveillance could offer a sentinel system if expanded to monitor other pathogens and boost public health preparedness. In the UK and USA, hospitals usually operate with specific geographic catchments for intake. Thus, NSS of hospital wastewater has great potential to offer the

sentinel system suggested by Diamond et al. (80), as the hospital represents a stratified snapshot of the local community. This information is useful as a warning for infection risk in congregate settings where a high degree of social interactions occurs(69) and can support specific community public health responses by prioritising socially applicable interventions relevant to each local community (i.e., testing, vaccine acceptability and community led public health activities)(81). Hospitals are distinctive with respect to NSS, since residents in most hospitals contribute regularly to the same wastewater stream with the exception of outpatients, visitors and staff (who do so intermittently) and, therefore, provide a representative indicator of disease cases, when paired with the comprehensive clinical surveillance data. It is probable that some of the most critically ill intensive care bedbound individuals could be precluded from contributing the WBS sample. This is because they can require diapers, sanitary systems, healthcare worker clean(82) or non-invasive faecal management systems (collection bags) which are disposed as biohazardous and incinerated offsite (83,84). A similar issue was discussed in school age children and workers who may be resistant to defecation in certain NSS contexts (schools and workplace respectively)(85,86), with important differences in defaecation practices emerging between countries and regions(87). Finally, evaluations of surveillance programs should be undertaken to understand the cost benefits of the program to feature not only the costs but also the benefits for population health and societal function. To summarise, it is suggested that monitoring hospital wastewater has numerous benefits, principally providing a public health sentinel as part of a cheap and easy to implement surveillance strategy. This approach could form basis of a risk-based approach to i) target investment to the areas where public health benefit is most realised, ii) reduce burden of nosocomial infections for current, (re)-emerging pathogen threats and antimicrobial resistance and iii) prevent outbreaks spreading from hospitals into community transmission. Future research should seek to quantify the social and ethical acceptability of WBS (especially near source or at source) when anonymity of individuals is not guaranteed (9) It is hypothesised that the benefits to hospitals will be substantial if WBS is implemented as part of a tiered

surveillance network. Careful engagement is needed to communicate results of wastewater data to the clinical community to better enable direct benefits to patient populations being sampled.

## Key points

- Wastewater provides anonymous and untapped disease data repository in hospitals
- In hospitals wastewater RNA-signal trends to nosocomial COVID-19 cases/outbreaks and is sensitive enough to detect new outbreaks
- Wastewater sampling can help to reduce hospitals' large scale clinical testing requirements as it is inexpensive
- Routine sampling using wastewater provides a platform for risk-based sampling and enables scaled resource allocation in response to outbreaks
- Hospital monitoring in low-income settings is a priority for future research.

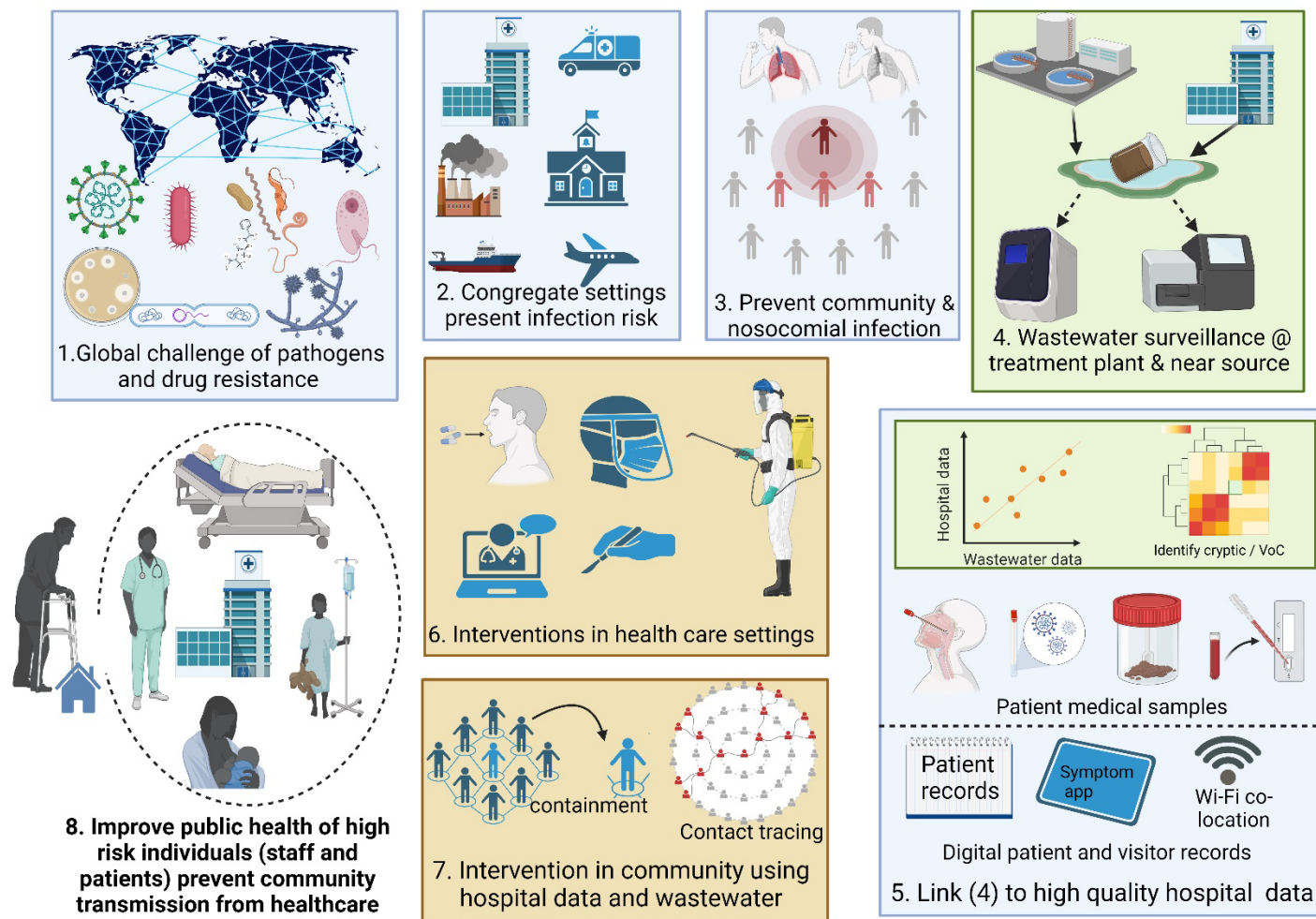


Figure 1 - Roadmap for using wastewater-based surveillance and near source sampling to better characterise infection risks in hospitals and care homes.

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## 3. Conflicts of interest

None

## 3. Data availability statement

There is no data associated with this review

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\* of special interest

\* \* of outstanding interest

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## **Wastewater-based epidemiology for surveillance of infectious diseases in healthcare settings**

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