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The potential of wastewater-based epidemiology as surveillance and early warning of infectious disease outbreaks

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Abstract
Infectious diseases caused by pathogens have become one of the main threats to public health. Efficient monitoring of infectious disease transmission is critical to prevent and manage infectious disease epidemics. Wastewater-based epidemiology (WBE) is an efficient approach with great potential for early warning of infectious disease transmission and outbreaks. By analyzing infectious disease biomarkers in wastewater taken from wastewater collection points, the transmission of infectious diseases in certain areas can be comprehensively monitored in near real time. This short review presents WBE as a surveillance and early warning system for infectious disease outbreaks regarding pathogens with pandemic potential. We also discuss the challenges and perspective of WBE in infectious disease surveillance and early warning.

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Infectious disease, Wastewater-based epidemiology, Pathogen, Early warning.

Introduction

Recently, the novel pneumonia (COVID-19) caused by the novel coronavirus (SARS-CoV-2) has rapidly spread worldwide and become a pandemic, despite city-wide quarantines and travel bans in many countries [1]. By April 15, 2020, 2,005,196 infections and 134,658 deaths have been reported in more than 210 countries. Humans have suffered several serious epidemics, including SARS, H1N1, Ebola, Zika, MERS, Nipah, and COVID-19, since 2000 [2,3]. These serious diseases caused by pathogens have made the effective monitoring of infectious diseases increasingly important.

Integral components of public health include strengthening the supervision of infectious diseases, realizing early warning and preventing infectious disease pandemics, especially emerging infectious diseases. There are many technologies to surveil the spatial–temporal characteristics of infectious diseases, such as sentinel surveillance, clinical-based surveillance, questionnaires or surveys, hospital admission data, and mortality and morbidity rates, which hold great significance for infectious disease surveillance [4]. However, most of these approaches depend on acquired data and information, such as incidence and mortality rates, prescription data, and hospitalization information, and herein, most of these systems are passive monitoring forms. Therefore, these techniques are subject to bias, resource insensitivity, detection blindness, and high cost [5]. Taking countries with limited health services as an example, the incidence rate may be higher than the assumed value because of a lack of access to health services [6]. There are blind areas for epidemic monitoring using traditional techniques. Because infectious disease testing is not available to everyone, potential patients and asymptomatic patients cannot be effectively counted and monitored, leading to an unknown extent of the spread. For example, it has been reported that approximately 60% of asymptomatic or mild SARS-CoV-2 infections may lead to a second outbreak [7]. Sometimes in serious epidemics, laboratory facilities are easily overburdened, and many cases are not reported. In addition, with the acceleration of global urbanization and the unprecedented growth in population, higher requirements are proposed for rapid health monitoring and response, which undoubtedly poses a challenge to the existing infectious disease monitoring and management system.

Therefore, novel monitoring and management approaches are needed for the prevention and early warning of infectious diseases. These technologies should be flexible, cost-effective, and scalable and should provide comprehensive and objective data in real time. Meanwhile, they also need to monitor multiple diseases, even rare diseases, in limited resource settings. Considering the current insufficient clinical and laboratory information [8], it is valuable to provide a novel surveillance and early warning techniques to compensate for the shortcomings of traditional tools/methods and to provide comprehensive and timely population exposure and disease results. Recently, wastewater-based epidemiology (WBE), which can provide objective and comprehensive real-time assessments of public and environmental health status, has developed rapidly.

As an effective health assessment approach, WBE has great potential for the prevention and early warning of infectious disease outbreaks for public health. Therefore, we first briefly introduce the principle of WBE and its wide application. Then, we discuss the feasibility of WBE in the supervision and early warning of infectious disease outbreaks caused by pathogens. Finally, we discuss the existing constraints and future perspectives in the field of WBE as an early warning of infectious disease epidemics.

The principle of WBE and its wide application

WBE is an integrated technique related to the extraction, analysis, data processing, and interpretation of targets (so-called biomarkers) excreted from feces/urine in wastewater, which provides comprehensive community health information. Untreated wastewater is obtained from wastewater collection points that serve communities located in clear geographical wastewater catchments. It is important that as a whole, the population contributes to the collection of wastewater from any wastewater collection point, and the wastewater from this community can be regarded as its collected urine. It is assumed that the identification and quantification of exogenous and endogenous biomarkers in community wastewater reflects the health status of the community population in real time. These biomarkers are derived from specific human excretions (such as metabolites or endogenous chemicals resulting from exposure to and/or disease) [9], as well as associated microorganisms/pathogens [10], which can reflect the health and living habits of the community because they contain rich biological and chemical information.

Since Daughton [11] first proposed the concept in 2001, WBE has achieved great success. He assumed that the analysis of drug residues in wastewater could be linked with population use [11]. Later, Zuccato et al. [12] achieved the goal of WBE for the first time in 2005 by successfully quantifying cocaine in wastewater to investigate cocaine consumption in the community. Since then, research on WBE has been conducted around the world [13]. Initially, the focus was entirely on the abuse of illicit drugs (http://www.emcdda.europa.eu/activities/wastewater-analysis), such as heroin [14], cocaine [15], ketamine [16], methamphetamine [13], and new psychoactive substances [17]. Most countries have monitored the use of illicit drugs through WBE for epidemiological studies. Notably, China uses WBE for practical policymaking and action related to drug control activity [18].

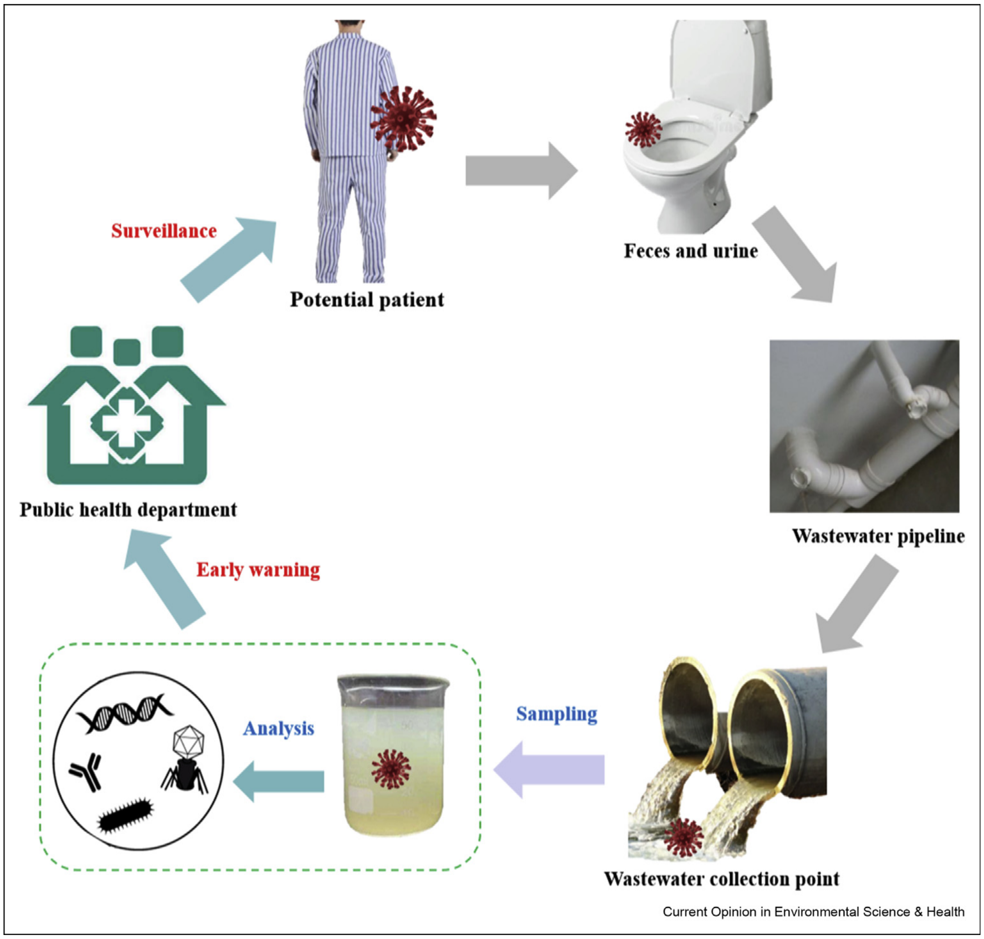
To date, apart from the evaluation of drug abuse, WBE has been expanded to various biomarkers [9], such as pesticides [5] and even heavy metals [19]. The scope of application of WBE ranges from the assessment of drug abuse and population health to the assessment of social, demographic, and economic correlates of food and chemical consumption [20]. WBE has also been successful in monitoring drug consumption, lifestyle choice, and population exposure.

Feasibility of supervision and early warning of infectious diseases using WBE

Some studies have discussed the future of WBE and expanded it to include biomarkers related to other aspects of public health, including diet, stress, and disease-related biomonitoring [5,21]. Owing to the wide variety of endogenous chemical and biological biomarkers related to diseases, the potential of WBE for monitoring infectious disease outbreaks and epidemic transmission at the community level is obvious [4].

WBE can be used as a complementary monitoring technique to provide rapid and reliable information about the population to inform the community about what diseases exist and help to monitor disease outbreaks (see Figure 1). When the presence of biomarkers is reported, the daily load in the wastewater is usually reported. In addition, to normalize cities of different geographical locations and population sizes to allow for comparison, daily load per capita can be reported. The back calculation process for biomarkers throughout the community can provide an unbiased response to key aspects of infectious disease information. In addition, not only can the spatial–temporal trends be determined but this information can also be monitored in real time to detect deviations from the general trend as early as possible. Owing to cost and logistical challenges, WBE provides advantages compared with biomonitoring technologies that focus on small target groups, as WBE is population wide and thus maintains the anonymity of individuals. Compared with other traditional surveillance systems, WBE can provide timely analysis, which can allow public services to respond quickly and adopt possible health interventions before infectious disease transmission and outbreaks.

Figure 1



Demonstration of WBE as a surveillance system and early warning for outbreaks of infectious diseases caused by pathogens. WBE, wastewater-based epidemiology.

Generally, for infectious diseases, it is important to obtain two pieces of information, namely, pathogen information and host–guest information, that is, some physiological indexes of infection [22]. The pathogenic information includes pathogens from bacteria, viruses, and other microorganisms that cause serious infectious diseases. Pathogen detection of wastewater influent could trace the source of pathogen carriers through pipeline backtracking, thus identifying the area of disease spread in the population. There have been many reports about virus determination in wastewater [23–26]. Wastewater analysis of polio has been used since the 1980s, when Finland [27] and Israel [28] successfully analyzed wastewater to assess the spread of polio. The World Health Organization has issued guidelines for monitoring polio in wastewater samples by environmental monitoring [4]. Wastewater analysis can also be used for retrospective prediction of the outbreak of hepatitis A and norovirus [29]. In terms of the COVID-19 pandemic, many scientists are trying to use WBE to detect SARS-CoV-2 in wastewater to screen potential virus carriers and provide early warning of COVID-19 outbreaks in the community [30].

Another important consideration is the host–guest information caused by infectious diseases, such as cough, blood protein, inflammatory, and immune information. For diagnostic purposes, urinary protein–based biomarkers are considered promising candidates for WBE [31], which is desirable not only because of the noninvasive nature of the test but also because it is a previously unexplored source of potential disease and health biomarkers [32]. The feedback of this information is related to protein-based inflammatory biomarkers, which are a group of important endogenous markers that are sensitive to changes in the body as early indicators of disease [33,34]. Apart from protein-based biomarkers, other human health biomarkers in wastewater, such as nucleic acids, have been reported [35]. For example, genetic information–related diseases can also be detected in wastewater [36]. It is believed that host—guest information related to infectious diseases in WBE will provide valuable new insights into community public health and have important implications for potential infectious diseases.

Challenges and perspective

Complex wastewater matrix

Although the principle of WBE is simple and provides an attractive advantage for public health monitoring, there are still some challenges to be considered. The first is that the wastewater matrix is complex. The biomarker concentration in wastewater is much more dilute than that in urine, and the wastewater substrate is a complex working environment [37]. As mentioned earlier, wastewater contains a wide range of chemical and biological substances that can provide incredible amounts of information about the population. However, one disadvantage of having such a large amount of information is that it must be successfully extracted from the matrix, and subsequent analysis of specific targets may be difficult. Taking protein-based biomarkers as an example, although it is generally believed that proteomics in WBE can provide valuable new insights into community public health, methods for the analysis of proteins in wastewater are lacking [31].

The complexity of the wastewater matrix is also challenging for pathogen detection. The main method for pathogen analysis is nucleic acid—based polymerase chain reaction (PCR), while there are various PCR inhibitors in wastewater, such as fat, protein, and other chemicals, that may affect subsequent PCR analysis. In addition, when DNA/RNA is extracted from PCR inhibitor—rich samples, the various commercial extraction kits sometimes show different efficiency and consistency [38,39]. This challenges meaningful comparisons across studies and the determination of spatial—temporal trends of pathogens.

To solve this problem, progress in molecular biology technology provides new methods for genetic material analysis, including digital PCR (dPCR) and next-generation sequencing technology. In dPCR, the absolute quantity of the target gene is calculated by dividing DNA/RNA samples into thousands of reaction wells and using Poisson distribution statistics. Owing to this distribution effect, when analyzed by dPCR, the effect of PCR inhibitors in wastewater is small [40]. Next-generation sequencing is another promising technology that provides substantial information about the complex microbial communities in the samples, such as the identification of various pathogens. Therefore, next-generation sequencing represents an important direction in the future. Extraction methods such as solid phase extraction (SPE) and immunoassay, as well as sophisticated analytical tools such as advanced mass spectrometry, have enabled the analysis of a large number of compounds [41]. In future development, more accurate and precise analysis methods are needed to obtain more infectious disease information from wastewater.

In addition, the ultimate goal of WBE is to achieve on-site monitoring and provide real-time data, which is also a guarantee of using WBE to provide early warning timeliness of infectious disease outbreaks. Analytical tools are required for simple, rapid, cost-effective, sensitive, selective, and multitarget analysis. The latest developments in sensor methods make field measurements possible so that the system can provide real-time infectious disease and public health information (see Figure 2). We also propose tracing COVID sources using an inexpensive and efficient paper-based biosensor [43]. At present, the research in this area is relatively weak, and only a few scientists have performed related studies [21]. This is an important challenge for WBE with a wide application of early warning of infectious diseases, and many more scientists should focus on this technical limitation in the future.

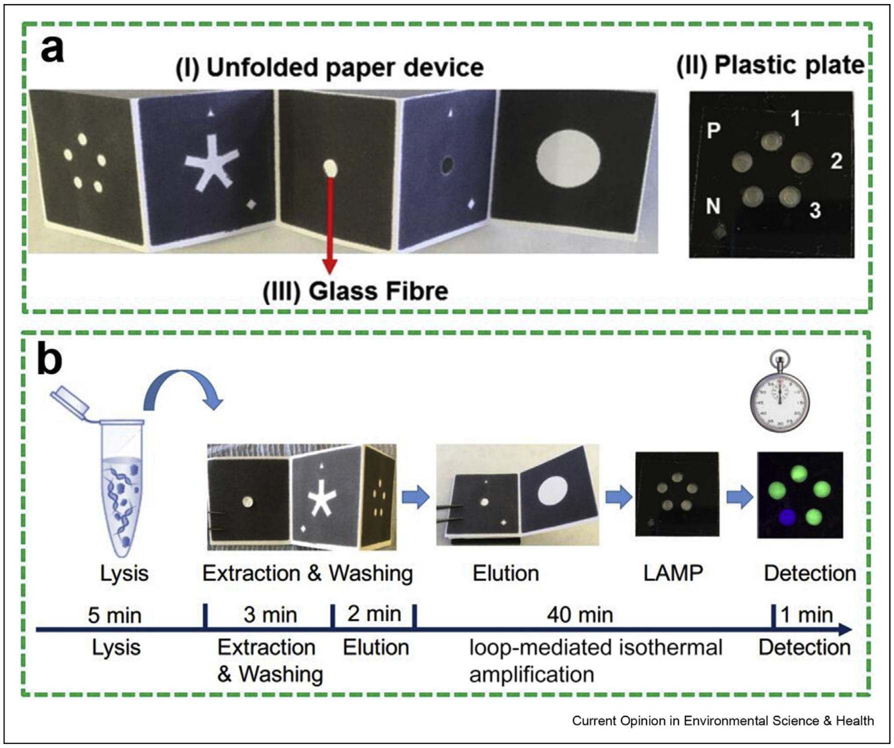
Desirable biomarkers

Apart from the aforementioned limitations, biomarkers in pipelines must be developed for infectious diseases, especially emerging infectious diseases. Endogenous and exogenous biomarkers, which can provide key information related to human health, have to be screened carefully. The biomarkers must be discharged through urine and feces and need to be specific to human metabolism. Ideally, the metabolic process involving biomarkers should be well understood to ensure that the biomarkers in wastewater are from human sources only, and not external sources [37]. The biomarker concentration must also be within a certain range to detect biomarkers in wastewater downstream [44]. Another important feature is that biomarkers must be stable, not only in wastewater systems but also during sampling and storage [45]. Therefore, it is important to find suitable biomarkers for specific infectious diseases and to determine their characteristics in wastewater, such as stability, for the application of WBE in the supervision and early warning of various infectious diseases.

Uncertainty about population size

Another challenge is that the uncertainty about the size of the population due to population fluctuation can cause problems in the monitoring of infectious diseases in wastewater because the presence of tourists or commuters in a catchment area may make it difficult to monitor the actual infectious diseases in the community [46]. For example, it is impossible to distinguish whether pathogens in wastewater originate from visitors passing through or from individuals within the community. There are several technologies that can be used to

Figure 2



Design of an integrated sensor for the detection of multiplex infectious disease pathogens. (**a**) Components of the sensor. (**b**) Illustration of the complete sample processing from sample introduction to pathogen detection. Adapted with permission from Yang et al. [36,42].

reduce sources of uncertainty related to population size, such as water chemistry parameters of mature analytical methods, which can help to estimate the population contributing to the catchment area of the wastewater collection points during a specific period of time [47,48]. However, the results are affected by the composition of wastewater, which leads to additional uncertainties related to these techniques, such as sample collection and analysis variability [46,49,50].

The presence of pathogens in wastewater, whether from catchment residents or not, still provides critical information, as members of the population may unconsciously come into contact with infected individuals. This may indicate possible diseases in the community, thus providing valuable time for proper preparation and response. However, we should objectively recognize the limitations of WBE and develop a reliable and standardized method to make the research more reliable and allow for comparison in the future.

Conclusions

It is generally believed that an effective monitoring system is the key to quickly intervening and controlling infectious disease epidemics. WBE shows great potential in providing complete health status information in a comprehensive and near-real-time manner at the community level. WBE can also be provided for the whole population to supplement current clinical data. Apart from the current global monitoring of COVID-19 in clinics and labs, if WBE is implemented, it could be used to track the source of the virus, identify the locations of potential virus carriers, and provide an effective early warning. Furthermore, if it is linked to an effective response system, WBE can be helpful for epidemic surveillance. However, to effectively apply WBE to infectious disease monitoring and early warning, much work remains for implementation on a larger scale, and rapid progress is needed to address some of the aforementioned key challenges. This work requires the cooperation of various related research fields. SARS-CoV-2 will certainly not be the last novel virus to emerge and seriously damage global public health. We hope that regardless of the identity of the pathogens that cause the next major outbreak, we can provide early warnings and effective epidemic supervision through WBE.

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Conflict of interest statement

Nothing declared.

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