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Discussion

Can wastewater surveillance assist China to cost-effectively prevent the nationwide outbreak of COVID-19?

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\textbf{GRAPHICAL ABSTRACT}

Monitoring sewage for the emergence of potentially dangerous viruses in China

\begin{abstract}
China has controlled the nationwide spread of COVID-19 since April 2020, but it is still facing an enormous threat of disease resurgence originating from infected international travelers. Taking the rapid transmission and the mutation of SARS-CoV-2 into consideration, the current status would be easily jeopardized if sporadic locally-transmitted individuals are not identified at an early stage. Clinical diagnosis is the gold standard for COVID-19 surveillance, but it is hard to screen presymptomatic or asymptomatic cases in those who have not exhibited symptoms. Since presymptomatic or asymptomatic individuals are infectious, it is urgent to establish a surveillance system based on other tools that can profile the entire population. Infected people including those who are symptomatic, presymptomatic, and asymptomatic shed SARS-CoV-2 RNA in feces and thereby endow wastewater-based epidemiology (WBE) with an early-warning ability for mass COVID-19 surveillance. In the context of China’s “COVID-zero” strategy, this work intends to discuss the practical feasibility of WBE applications as an early warning and disease surveillance system in hopes that WBE together with clinical testing would cost-effectively restrain sporadic COVID-19 outbreaks in China.
\end{abstract}

1. Introduction

Although COVID-19 remains highly transmissible around the world, China has controlled the nationwide spread of COVID-19 and has gradually returned to normal since April 2020. Nonetheless, after the relaxation of containment measures such as restrictions on national and international travel, COVID-19 outbreaks triggered by infected international travelers...
or even contaminated imported goods (Pang et al., 2020) have intermittently occurred in megacities (e.g., Beijing, Shanghai, and Guangzhou) as well as in small and mid-sized cities (e.g., Zhangjiakou, Putian, and Dalian) in China. The risk of the resurgence of COVID-19 nationwide remains high if any sporadic outbreaks are not controlled at an early stage.

China’s infectious disease surveillance system was established after the emergence of severe acute respiratory syndrome (SARS) in 2003. This system includes the National Notifiable Infectious Disease Surveillance System, the Public Health Emergency Event Surveillance System, and China Infectious Disease Automated-alert and Response System. This monitoring and early warning of infectious diseases system is based on a case reporting system that covers all levels of healthcare facilities across the country. Confirmed case reports from local hospitals are directly sent to the aforementioned three systems in a timely manner via the internet, whereas for serious and unknown infectious diseases, the clinical diagnosis should be reported within 2 h via telephone or fax (Cao et al., 2020). However, for COVID-19, a substantial proportion of infected people barely exhibit symptoms whereas healthy people can be infected by symptomatic and asymptomatic individuals. Thus, an early warning of COVID-19 outbreaks in communities is limited when merely based on the current symptom-based disease surveillance system. As a result, China has undertaken stringent containment strategies such as quarantines and lockdowns once a few domestic infected individuals have been reported in a community. To rapidly identify and isolate virus carriers, China offers free clinical/laboratory testing to all residents, which greatly expands the application scale of COVID-19 diagnostic testing. Based on the evidence of a few daily confirmed cases reported by the National Health Commission of China, these control measures are effective in reducing human–to–human transmission.

Despite this enormous achievement, it is argued that such “COVID-zero” containment measures not only require a large input of various resources for mass testing and lockdowns, but also stall and interfere with the recovery of the society and economy, notably in service sectors such as retail and tourism (Wang et al., 2021b). The rapid transfer from a time of peace to civil defense also challenges the emergency management capability of local governments, because it is difficult to carry out the strict containment measures over a long period of time without making any mistakes. As reported by Zhou et al. (2021), a cabin cleaner working at Nanjing Lukou Airport was the first locally transmitted case during the COVID-19 outbreak in Nanjing, Jiangsu Province, in July 2021, who was infected after cleaning an international aircraft carrying infected passengers. Due to the lenient management at the airport, COVID-19 first circulated among the airport cleaning staff and then was introduced to domestic passengers, families, and the local communities, which consequently led to large-scale community transmission and eventually spilled over to nine cities across the country. Hence, local governments are asked to maintain vigilance and improve disease control strategies. Moreover, the identification of the spread of COVID-19 in rural areas is a tricky issue, which was indicated by cases of cluster transmission in rural areas in Fujian Province. As reported by the National Health Commission of China, the disease was introduced to villagers through one returning citizen who may have become infected during quarantine but was not detected for at least ten days. Consequently, the risk between rural and urban areas in public health facilities as well as the level of clinical diagnosis and treatment (Yao et al., 2020), local government has to perform regular mass testing to rapidly screening infected individuals from healthy people. Therefore, an effective, timely, and economical alternative for monitoring and early warning system is critical for controlling and preventing the nationwide spread of COVID-19.

Wastewater-based epidemiology (WBE) is an environmental surveillance method that quantitatively analyses the concentration of specific chemical/biological markers at wastewater treatment plants (WWTPs) to estimate the lifestyle or public health status in communities (Ma et al., 2020a). Since Dutch researchers first reported the discovery of SARS-CoV-2 in domestic wastewater (Medema et al., 2020), many countries have explored the possibility of an early warning and surveillance system for COVID-19 based on WBE (Hayward, 2020; Thompson et al., 2020). However, few studies have focused on the application of WBE in China as an alternative way to prevent the resurgence of COVID-19. Therefore, this work aimed to discuss the practical feasibility of establishing a complementary surveillance system for communicable diseases such as COVID-19 in China.

2. The principle of WBE and its application

The concept of WBE was firstly proposed to estimate the illicit drug consumption in communities (Daughton, 2001). In 2005, the cocaine consumption in Italy was estimated through WBE for the first time and thus verified its practical feasibility (Zuccato et al., 2005). Since then, extensive studies have been conducted to trace various target substances such as drugs, alcohol, nicotine, pharmaceuticals and personal care products (PPCPs), antibiotics, and viruses, as summarized in Lorenzo and Pied, (2019). Generally, epidemiological investigations based on WBE follow a procedure of pre-investigation, sampling, marker selection, pre-treatment, instrumental analysis, and back-estimation based on modelling.

Since the outbreak of the COVID-19 pandemic, the adoption of WBE has been accelerated to monitor the prevalence of highly infectious diseases in communities or even in residential buildings (Wong et al., 2021). After the detection of SARS-CoV-2 in the feces or urine of infected individuals (Tang et al., 2020), the discovery of SARS-CoV-2 in domestic wastewater was reported in many countries (Ahmed et al., 2020a; Haramoto et al., 2020; Kumar et al., 2020; La Rosa et al., 2020; Medema et al., 2020; Sherrchan et al., 2020). Because the concentration of SARS-CoV-2 RNA in wastewater increases with the number of infected people, it becomes possible to determine hotspots of COVID-19 in communities at an early stage and to monitor its spread through WBE. Australia, the Netherlands, the United States, and many other countries are now exploring how to establish an early warning system for public health emergencies based on WBE (Hayward, 2020; Thompson et al., 2020; Meng et al., 2021). Compared with conventional epidemiological investigation approaches (Table 1), WBE, without individually testing thousands of people, is regarded as a cost-effective and real-time method to monitor the spread of COVID-19 within the corresponding wastewater catchments.

3. The application of WBE in China and its practical feasibility

Similar to other countries, previous studies of WBE in China were initiated to investigate the illegal consumption of illicit drugs such as cocaine, heroin, and methamphetamine. In 2013, Lai et al. first utilized WBE to quantitatively evaluate the daily use of four illicit drugs in Hong Kong (Lai et al., 2013). In 2014, Khan et al. reported the first application of WBE in monitoring the consumption of various drugs in megacities such as Beijing, Shanghai, and Guangzhou in mainland China (Khan et al., 2014). Since then, several Chinese research groups have investigated the consumption of illicit drugs, tobacco, nicotine, and PPCPs in various cities across the country. Nonetheless, previous studies focused more on the

Table 1

| Characteristic                      | WBE          | Conventional approaches |
|------------------------------------|--------------|-------------------------|
| Time                               | Rapid        | Time-consuming          |
| Cost                               | Low          | High                    |
| Objectivity                        | Yes          | No                      |
| Real-time                          | Yes          | No                      |
| Early warning                      | Yes          | No                      |
| Consumption variation in a short-term period | Yes          | No                      |
| Predictive                         | Yes          | No                      |
| Trends of target substance consumption | Yes          | No                      |
| Location                           | Yes          | Yes                     |
| Frequency of drug consumption       | No           | Yes                     |
| Purity and price of the target substance | No           | Yes                     |
| Demographic characteristics         | No           | Yes                     |
| Usage of drugs                     | No           | Yes                     |
| Factors affecting consumption      | No           | Yes                     |
verification of WBE in supporting epidemiological surveys, whereas a nationwide monitoring system has not yet been established.

Because WBE could indicate a COVID-19 outbreak in communities or in residential buildings a few days to a week before the onset of symptoms for an individual patient (D'Aoust et al., 2021; Wong et al., 2021), an initial spike in infection would be rapidly detected by the continuous collection of wastewater samples and the analysis of the concentration of SARS-CoV-2 RNA therein. Based on the initial WBE result, local governments could conduct further clinical testing or quarantine people at COVID-19 hotspots within communities to prevent the transmission of the disease without affecting the normal activity of the entire population of the whole city. In other words, WBE together with clinical testing could help China to fight COVID-19 more efficiently and cost-effectively.

To elucidate the feasibility of WBE, we mainly focused on the sewage and drainage system and laboratory testing capabilities in China, which are two prerequisites for WBE implementation. A well-functioning sewage and drainage system, especially the coverage of the drainage systems in communities, is a prerequisite for applying WBE. With the rapid development of urbanization, WWTPs in China receive a large volume of domestic wastewater from cities and towns, which is essential for the implementation of urbanization, WWTPs in China receive a large volume of domestic wastewater from cities and towns, which is essential for the implementation of sewage treatment. As shown in Fig. 1a, the treatment capacity and the total length of the drainage pipeline have increased significantly over the past two decades. According to the National Bureau of Statistics of China, by the end of 2018, the daily capacity of sewage treatment reached to 181,452 million m³/d, whereas there were 10,826 WWTPs with an authorized discharge permit by November 2020. By the end of 2018, the total length of the sewage pipeline in China reached 683,435 km. However, as indicated in Fig. 1b, the allocation of the pipeline across the whole country is unbalanced. The drainage system coverage was relatively high in the eastern part of China such as in Jiangsu and Zhejiang Province, whereas it remained low in the western part such as in Tibet and Qinghai Province. Despite this, the drainage system coverage in large and mid-sized cities in China is >90% with a pipeline density of 9.6 km/km², which basically meets the requirement of WBE.

Moreover, most WWTPs in China now regularly auto-sample and analyze the flow rate, pH, COD, and ammonia concentration of the influent wastewater (Gao et al., 2015), which shows the practical feasibility of the implementation of WBE in the sampling and analysis process. For analytical capabilities, there are more than 200 laboratories nationwide that are equipped with sophisticated instruments for the analysis of chemical or biological markers, such as digital PCR and liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Gao et al., 2015). For SARS-CoV-2 analysis, China has >40 Biosafety Level 3 laboratories and 2 Biosafety Level 4 laboratories that are affiliated with the provincial CDC as well as academic institutes (Wu, 2019; Ministry of Education of the People’s Republic of China, 2020). After the outbreak of COVID-19, China further strengthened its capability for the management of public health emergencies, according to the National Development and Reform Commission. The central government launched a promotion program in May 2020 to establish more laboratories across the country with a biosafety level higher than Level 2 (The National Development and Reform Commission, 2020). The analytical abilities for applying WBE at the national level could be sufficient in the near future. Hence, the implementation of WBE would become easier with hundreds of local research centers and laboratories that are equipped with various chemical and biological analysis instruments.

SARS-CoV-2 has been detected in environmental samples like sewage and silt in Huanan Seafood Market as well as in the disinfectant effluent discharged from hospitals in Wuhan, the epicenter of the first wave of COVID-19 (Zhang et al., 2020; Gao et al., 2022). Zhao et al. (2022) further reported that the concentration of SARS-CoV-2 RNA was approximately 7.4 × 10^{10} copies/L in the influent wastewater of WWTPs in Wuhan. Yang et al. (2022) also found SARS-CoV-2 RNA in both sewage systems (8.5 × 10^{8}–8.8 × 10^{9} copies/L) and river water (8.5 × 10^{7}–9.52 × 10^{8} copies/L) in Beijing after its local outbreaks in 2020. Because the sampling period of these studies were almost at the end of the epidemics, it is impossible to perform back-estimation modelling for the comparison of the WBE results and the clinically confirmed cases. Nonetheless, the success in the detection of SARS-CoV-2 RNA in the relatively low range further strengthened the practical feasibility of WBE for COVID-19 monitoring in low prevalence areas. Moreover, the experience from Hong Kong in the WBE implementation (Xu et al., 2021; Zhang and Chui, 2021) could also be helpful for megalities in mainland China to establish their early warning system of COVID-19 based on WBE. Thus, it is reasonable to conclude that the application of WBE for infectious disease monitoring and early warning systems is technically feasible in China, notably for large and mid-sized cities with well-developed municipal infrastructure.

4. Challenges and suggestions

Although WBE has been shown to be a powerful epidemiological investigation approach in the mass surveillance of COVID-19, there are several limitations and challenges in establishing an alternative disease surveillance system for public health emergencies, such as COVID-19. Currently, there is no consensus regarding the framework of sampling, pretreatment, analysis, back-calculation, and modeling for the implementation of WBE in COVID-19 surveillance (Michael-Kordatou et al., 2020). Previous studies in the literature (Wang et al., 2016; Ahmed et al., 2020b; Li et al., 2021) have already pointed out that the reliability of the WBE results is significantly affected by uncertainties occurring at every step in the whole procedure of the implementation of WBE. Meanwhile, since little is known about the transfer and fate of SARS-CoV-2 in sewage, a chemical/biological marker for SARS-CoV-2 is still lacking (Giacobbo et al., 2021;
Michael-Kordatou et al., 2020; Tran et al., 2021). Most of the previous studies in the literature directly analyzed the concentration of viral SARS-CoV-2 RNA copies in the sample by RT–PCR, as summarized in Meng et al., 2021. However, this approach not only requires sophisticated instruments but also increases the potential transmission risk for laboratory staff. In other words, the lack of a suitable marker for infectious disease may limit the future application of WBE. Recently, various novel analysis approaches have been proposed to detect SARS-CoV-2 in wastewater, such as a paper-based wastewater testing device and a nanoparticle-based sensor array for the detection of SARS-CoV-2 (Mao et al., 2020b; Safiabadi Tali et al., 2021; Alafeef et al., 2022). These approaches may support the future application of WBE in monitoring emerging communicable diseases in wastewater and could be extremely useful for less-developed countries and regions in monitoring COVID-19 hotspots rapidly and efficiently. Another important factor that should be taken into consideration for the back-estimation modelling of WBE is mass migration in China, especially during national holidays such as the Spring Festival. With the growth of national high-speed railways, it has become convenient to travel across the country in several hours, thus resulting in frequent population migration. Population migration not only allows infectious diseases to circulate rapidly but also leads to difficulty in tracking carriers of the virus. Thus, Liu et al. (2021) proposed to set-up more sampling points to narrow the disease surveillance in the community level. They also suggested that the viral RNA of SARS-CoV-2 obtained in the samples could be used for genome sequencing to determine its original source, whether from transient or permanent residents in the community, by comparing the previous data of other regions. Wu et al. (2021) has proposed a technical framework of WBE recently, but more efforts are still needed to build a standard protocol of the implementation of WBE.

Furthermore, the drainage pipeline system and its topology may influence the accuracy of WBE results. Since the back-estimation of disease prevalence is based on the measured concentration of the chemical/biological marker in a wastewater sample, the evolution of the marker in drainage systems from households to WWTPs is critical. Prior to 1990, China adopted a combined sewer system (CSS) rather than a separated sewer system (SSS) (Gao et al., 2015). As a result, domestic wastewater, rainwater, and treated industrial wastewater are discharged together into WWTPs via the same drainage pipeline system, notably in old towns. The complicated composition of sewage in a CSS may cause difficulties in the sample pre-treatment and analysis steps of WBE, whereas the marker concentration may be diluted when relatively clean rainwater flows together with domestic wastewater. Moreover, because the operation, management, and maintenance of the drainage system have not drawn much attention in China, serious problems within the drainage system occur in many cities, such as leakage, overflow, and blockages. The exfiltration and infiltration of drainage networks result from corrosion or structural damage of the pipeline, pipe misconnection and mixed connection, and backwards irrigation from surface water (Cao et al., 2019; Wang et al., 2021a), which results in a lower concentration of the marker in the influent of WWTPs than that at the starting point of the pipeline network. Although the lifetime and evolution of SARS-CoV-2 in a drainage system remains unclear, a previous study has revealed that 50% of the initial COD, BOD and NH$_4^+$ were lost during the transport of wastewater from households to WWTPs in China (Cao et al., 2019). In addition, chemical and biological markers can be retained in pipelines owing to physical deposition and sedimentation. Recent studies (Zhao et al., 2022; Yang et al., 2022) found that retained markers such as SARS-CoV-2 RNA may re-emerge in wastewater due to continuous flushing in pipelines. All these issues would result in fluctuations in the marker concentration and finally affect the accuracy of WBE results, which need further systematic studies.

In the past two decades, China has experienced two coronavirus-induced epidemics (i.e., SARS and COVID-19). To cope with the future challenges in public health emergencies, it is vital to monitor sewage for the emergence of potentially dangerous viruses based on WBE and to establish a corresponding surveillance system that is complementary to the current case reporting system. Based on the current status of wastewater systems in China, it is impossible to offer a “one-size-fits-all” solution for the implementation of WBE. Under the context of the “COVID-zero” strategy, an early warning system based on WBE as sentinel surveillance should be prioritized at critical locations, such as airports, quarantine hotels, and fever clinics, while the monitoring scale would be enlarged for communities with a high population density. Rather than launching a national wastewater surveillance program, we think it would be feasible to initiate WBE monitoring in megacities, traffic hub cities, and well-developed coastal cities with a high population density. As demonstrated in Fig. 2, we suggest (a) setting up local sampling points at places with high potential risk such as seafood markets, hospitals, public toilets, airports, and bus and train stations, (b) establishing a standard protocol for WBE, ensuring the accuracy and reliability of WBE results, and (c) utilizing automatic sampling and analysis equipment in the sewage systems within communities. With the assistance of “Smart City” and 5G technology, the analyzed data would be collected and processed in real time. As a result, local and central governments could formulate and adjust containment strategies based on the scientific and reliable estimations from both WBE and clinical results.

![Fig. 2. Schematic diagram of the implementation of WBE in China.](Image)
5. Conclusion

Because the detection of SARS-CoV-2 in wastewater can be several days prior to the onset of symptoms, WBE profiling both healthy and sick people in communities could provide reliable and accurate data for policy makers to mitigate disease appropriately and effectively. There is no reason to replace clinical testing with WBE, but the advantage of WBE in epidemiological investigation such as early warning is worthy of implementing in China. With the rapid development of the sewage system, it is feasible for China to apply WBE in monitoring the outbreak of infectious disease, especially in the well-developed coastal cities with a high population density. Thus, we recommend that WBE would assist China to cost-effectively control and prevent the spread of infectious disease in communities in the near future. The promotion of WBE applications in China may also provide useful information and experience for many other developing countries with an underperforming sewage system.

CRediT authorship contribution statement

Z.Y.: conceptualization, funding, writing—original draft, and review and editing. K.Z., W. H., Z. G., S. J., and C. Z.: data collection and formulation, figures, and writing—original draft. Y.Y.: conceptualization and review and editing. All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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.

Acknowledgments

This work was supported by the Natural Science Foundation of Fujian Province (No. 2021J05132) and the Educational Research Project for Young and Middle-aged Teachers in Fujian Province (JAT200061).

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