



## Opinion



# Infectious Disease Surveillance in Vietnam: Pathogen Early Detection in Hanoi Wastewater

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## Introduction

Since the dawn of civilization, infectious disease pandemics have periodically threatened humanity. Newly emerging and re-emerging pathogens continue to challenge global public health in the twenty-first century. Most of these have been first detected in locations in close proximity to wildlife, from which the microbial pathogen may have jumped to a human host,<sup>1</sup> or which may serve as environmental reservoirs of zoonotic infections.<sup>2</sup> The Southeast Asian country of Vietnam has an exemplary recent record of infectious disease control and prevention, successfully containing viral pandemics of the original severe acute respiratory syndrome (SARS) in 2002,<sup>3</sup> influenza H1N1 in 2009,<sup>4</sup> and the first wave of Coronavirus disease 2019 (COVID-19) in 2020.<sup>5</sup> Nevertheless, despite the widespread availability of several vaccines effective against previously predominant variants of SARS coronavirus 2 (SARS-CoV-2), the potential emergence of novel variants that could have greater infectivity, transmissibility, and/or immune evasion, continues to threaten the wellbeing of Vietnamese people as well as global public health.<sup>6</sup>

Monitoring the advent and prevalence of SARS-CoV-2 variants of concern and variants of interest in a community could help local health authorities to make informed decisions in the best interests of the population's health.<sup>7</sup> Since the onset of COVID-19, pre-sewage treatment wastewater sampling has been harnessed as a non-evasive large-scale pathogen surveillance tool.<sup>8</sup> Wastewater surveillance complements clinical diagnosis because between 7–14 days' early warning detection of transmission by asymptomatic infected individuals is achieved without excessive resources and labor required for frequent human testing by an approved diagnostic microbiology laboratory. The level of sensitivity of SARS-CoV-2 detection in sewage currently approximates to one in 2,000 people,<sup>8,9</sup> thereby being sufficiently accurate to identify

the location of an urban outbreak to a close geographical proximity or large building occupancy.

The establishment of infrastructure for wastewater-based SARS-CoV-2 surveillance would serve as an entry point for monitoring other pathogenic infectious agents (of viral, bacterial, fungal, and parasite origin) in resource-limited settings.<sup>10</sup> This approach could provide a more rapid and accurate early warning system for the outbreak of notifiable infectious diseases than more traditional public health surveillance systems. Furthermore, this technology would enable medical researchers to investigate horizontal transfer among enteric bacterial isolates of antimicrobial resistance (AMR) genes,<sup>11</sup> and even to detect chemicals or biomarkers that humans excrete during the course of infectious or metabolic diseases.

## Research questions

While the scale of a pandemic is global, its transmission occurs locally. In order to prevent an outbreak from potentially escalating to become a pandemic, we must understand local transmission. Therefore, surveillance should be designed around local contexts. How to identify sentinel sites for wastewater surveillance is an important exploratory research question. The determination of sentinel sites and the frequency of sampling would depend on specific, actionable surveillance goals. These would require a different approach in a public health crisis to endemic conditions. Examples of key research questions are listed below:

What factors (past infectious data, seasonality, human mobility, human behavior, population density, number of houses served by a sewage pipe, and others) guide sentinel site selection?

How do the natural history of pathogens, their life cycles, and disease transmission influence the locations and frequency of sampling?

How can we establish a surveillance system that can capture an outbreak's evolution and thereby help to prevent its escalation to an epidemic, pandemic, and eventual endemicity, and to evaluate the effectiveness of public health interventions?

How can we accurately predict hotspots of infection and transmission routes (e.g., large apartment complexes, airport terminals, public transportation hubs, school buildings, office blocks, shopping malls, and venues of public gatherings)?

How can we use artificial intelligence-assisted tools to assess

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**Abbreviations:** AMR, antimicrobial resistance; COVID-19, Coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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potential transmission and to identify sentinel sites?

What are the minimum personnel, infrastructure, and budgetary requirements to implement a supervised artificial intelligence approach for the wastewater surveillance of microbial pathogens and AMR genes?

How can we use such surveillance findings to accurately inform the effective implementation of public health interventions?

## Research approach

Resolving these pressing issues would require adoption of an integrated, unifying ‘One Health’-style approach and fostering of interdisciplinary research between environmental engineers, medical microbiologists, public health physicians, epidemiological modelers, and computational scientists. This would facilitate a functional surveillance system to be informed by modeling of transmission.

By installing autosamplers to collect composite samples, the sewage surveillance system could be tested for high-rise residential buildings in selected districts of Hanoi, the capital city of Vietnam. Our pilot investigations showed a range of access points located proximately to the piped sewage supply to which locally made, low-cost, remotely controlled autosampling devices may be custom fitted. Composite sampling involves taking a small volume of sewage from each pipe (e.g., 10–200 mL) every hour for 24–72 h. This method allows the collection of samples over time to capture the unpredictable release of human body waste.<sup>8</sup> The composite sewage concentration is standardized for processing and analysis by dividing the volume of sedimented sludge by the total volume for each collected sewage sample. For SARS-CoV-2, the sampling of respiratory material, serum, or urine on alternate days is necessary to identify positive individuals with more than 90% sensitivity during their infectious period in individual-level polymerase chain reaction (PCR) testing.<sup>12</sup> Therefore, this should provide adequate sensitivity to detect any cases using wastewater (which would contain urine, possibly plus other specimen types). The samples would be assayed in a one-step, closed system for amplification and detection by a multiplex quantitative real-time PCR using a SARS-CoV-2 variant and other pathogen-specific primers.<sup>13</sup> For the validation of a positive result, synthetic sequencing would be performed to determine the precise variant detected (e.g., on an amplicon of a non-conserved region).

A hierarchy of epidemiological models can be developed to investigate the spread of infection in each community and hence to guide the surveillance. Model predictions inform testing deployment, increased testing frequency to target clusters of infection, and spatial distribution of wastewater sampling to preemptively act on propagating infection waves. The multi-community spatial-temporal nature of the model balances accuracy with computational cost and provides sufficient flexibility to respond to near real-time data, thus adapting accordingly to provide an ensemble forecast that guides decision-making.<sup>14</sup> These models and the sewage surveillance system would be complemented by human testing. For example, a ‘susceptible-exposed-infectious-recovered’ model based on the mass rate of SARS-CoV-2 RNA in wastewater to predict the number of infected individuals could be compared with the number of confirmed cases identified by local health authorities for the identical geographical area over the same period.<sup>15</sup> Information on extraneous variables that may influence sampling at a given site and time would also help to build a detailed picture of the multifactorial circumstances under which pathogen transmission occurs. For instance, heightened population mobility during holiday seasons, festivals, and other mass gatherings, affects the

magnitude of transmission of COVID-19.<sup>16,17</sup> Thus, surveillance could better inform predicted transmission rates, thereby helping public health policymakers to plan for periods of peak travel, overcrowding, and hence decreased social distancing.

The primary aim of initial trials is to establish a sewage surveillance system capable of quantifying SARS-CoV-2 and its variants of concern. Virus quantification is crucial because variants have different transmission capabilities. Moreover, low prevalence detection of viral RNA fragments of a variant with high transmission capability, such as Omicron, provides an early warning sign of introduction and potential spread in a community. Quantitative results (instead of positive/negative) are also important as the trend in genome concentration enables prediction of future transmission levels. Proof-of-principle preliminary results showed the transferability of this technology, developed in a rural US setting,<sup>9</sup> to an urban Vietnamese context, with comparable sensitivity and specificity of detection of SARS-CoV-2 in wastewater samples.<sup>18</sup>

The secondary aim is to develop infection models that could account for: (1) heterogeneous biological and social susceptibility to the disease; (2) emergence of new SARS-CoV-2 variants of concern that might exhibit enhanced transmission; and (3) vaccination coverage. This adaptive modeling strategy is calibrated continuously using the available data from the sewage surveillance system and additional statistics on hospitalization, intensive care unit occupancy, and cause of death. As more information emerges on the post COVID-19 condition, also known as long COVID,<sup>19</sup> other health metrics, such as disability-adjusted life years (DALYs) may be incorporated into refined models.

## Novelty and impact

This approach enables a near real-time evaluation of the epidemic status in each local community, short-term prediction of the course of the epidemic, and informs guidelines for longer-term mitigation. A follow-up aim focuses on understanding the prevalence and emergence of AMR in these Hanoian communities. AMR, particularly the rise in antibiotic-resistant bacterial pathogens, is a worsening silent pandemic.<sup>20</sup> Increased usage of prescribed antibiotics, rapidly driving resistance to these, has been reported for severe COVID-19 patients.<sup>21</sup> As a consequence, the prevalence of SARS-CoV-2 is likely to exacerbate AMR worldwide, especially in Vietnam where direct accessibility of consumers to pharmacies has led to the overuse and abuse of antibiotics.<sup>22</sup> The emergence of AMR happens primarily in the community, from where it is brought into clinics and hospitals, especially in a setting like Vietnam where antibiotic usage is not regulated.<sup>22</sup> In general, medical doctors only see a small proportion of patients who take antibiotics, mostly those severe cases that require specialist referral or hospitalization. Importantly, the community surveillance technology that has been outlined here has the potential to improve antimicrobial stewardship and thereby to preserve the life-saving power of current antibiotics.

The dual surveillance of SARS-CoV-2 and AMR genes in bacteria (both pathogens and commensals) is relevant to enhancing our understanding of both viral and bacterial epidemiology. Our preliminary data have shown the presence of several AMR genes in both clinical (blood and tissue) specimens and sedimented sewage samples collected in sites in Hanoi.<sup>18</sup>

## Future directions

For the long-term monitoring of the Vietnamese population of al-

most 100 million people, a non-invasive, privacy-preserved tool for community-wide epidemiological surveillance of pathogen transmission and AMR horizontal gene transfer should be developed. The described infectious disease surveillance method is inexpensive compared to large-scale testing and would be suitable for resource-limited settings. Additionally, it could be used to disseminate information via an artificial intelligence smartphone application both to alert for outbreaks and to diagnose earlier and therefore better treat incidence of infectious diseases. Data should be publicly accessible to inform patient-centered decision-making on notifiable diseases by relevant community stakeholders, such as the Ministry of Health of Vietnam, public and private hospitals in Hanoi, and local healthcare professionals.

Only around one-fifth of Vietnamese wastewater is treated, predominantly in the two largest cities of Hanoi and Ho Chi Minh City (formerly Saigon), the remainder being released directly to the environment. This means that surveillance in critical locations outside modern, metropolitan areas would also be important and should form an integral part of any future national reporting network. Furthermore, it is worth noting that this method could be applied to monitor veterinary pathogens and to detect AMR in livestock and wildlife. This opens the future possibility of its use in a 'One Health' context.

## Conclusions

The proposed early warning surveillance system would provide best practice preparedness for the possible emergence of a more infectious and pathogenic SARS-CoV-2 variant. In order to avoid a surge in cases that might otherwise occur, it is essential to implement this or a similarly innovative 'future-proofing' response strategy. By its integration into a coordinated 'preparation, response, recovery' policy alongside existing social distancing measures and vaccination campaigns in Vietnam,<sup>17</sup> this would help to control not only COVID-19, but also to take a proactive approach to other infectious diseases of public health concern to the country. In this way, the nation can regain its position held during the first 18 months of COVID-19 as a global leader in pandemic control.<sup>23</sup> By Vietnam exploring the development of this infectious disease surveillance system, the lessons learned could be heeded for subsequent implementation in other low- and middle-income countries.

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## Conflict of interest

The authors declare no conflicts of interest.

## Author contributions

Article conception (AWT-R and THN); literature search and data

collection (AWT-R and THN); interpretation of information (AWT-R and THN); writing - original draft preparation (THN); writing - manuscript preparation (AWT-R); writing - editing critically for important intellectual content (AWT-R and THN); AWT-R and THN have made a significant contribution to the preparation of this article and have approved submission of the final manuscript.

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