Defining a research agenda for environmental wastewater surveillance of pathogens

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Environmental surveillance, defined as the systematic collection of samples and associated infectious disease pathogen data from wastewater for the purpose of informing decisions, has a rich tradition in public health. High-resource settings such as the US[1] and Europe[2] have started to implement environmental surveillance networks for use of multi-pathogen data from wastewater, including for pandemic preparedness. Implementing environmental surveillance in lower-resource settings, where a large proportion of populations live in houses not connected to convergent sewer systems, has lagged due to epidemiological and resource challenges. Correcting this imbalance is important to ensure equitable access to actionable surveillance.

The Bill & Melinda Gates Foundation hosted a meeting in May 2022, bringing together academic, manufacturing, and public health decision-making partners to co-develop a vision for multi-pathogen environmental surveillance, which we report on here. Environmental surveillance could complement clinical surveillance by potentially supporting the detection of multiple pathogens within a single surveillance network at a fraction of the cost of case-based surveillance per capita. During our discussions we focused on seven pathogens that were proposed by the group: poliovirus, *Salmonella typhi*, *Vibrio cholerae*, SARS-CoV-2, Hepatitis A and E, and Measles virus. For each of these pathogens, relying on only clinical surveillance to generate actionable data is a challenge for a number of reasons, including a low ratio of symptomatic cases to overall infections (as seen in polio), a lack of gold standard diagnostic technology broadly available (such as for typhoid, cholera, Hepatitis E, and Hepatitis A), and inefficiency of genomic sequencing at the clinic level (which has been the case for SARS-CoV-2 and measles).

Optimal sampling sites, frequency, and methods will vary depending on the specific goal of the surveillance program and the pathogen of interest[3]. Whilst well-mapped sewage networks with enumerated populations can inform sampling site selection in some regions, hydrological maps overlayed with data sets for elevation, bluelines, and population (such as those from WorldPop[3,4]) are necessary in low-resource settings where open drains or riverine networks receive human waste directly from households. In these areas, site selection approaches are often iterative, due to uncertainties in the data available and connectivity of the networks.

Sampling frequency can vary depending on the inference required. Modelling has shown monthly collections to be sufficient for poliovirus detection, [5] but early warning systems, as desired for SARS-CoV-2 and *Vibrio cholerae*, could require weekly or potentially even more frequent sampling to inform public health action in a timely manner [6,7]. Sampling frequency may also be driven by: the cost of sampling; travel to and from sites; cold-chain costs; and the capacity of the laboratory to test samples.

Choice of sampling method can be driven by the need for sensitivity versus quantitative measurement. Passive or trap sampling (such as using Moore's swabs[8]) can effectively allow greater flow volumes to be sampled but can be difficult to translate to quantitative measurements. Grab samples, by contrast, provide an absolute sampling volume, potentially facilitating quantitative measurements, but sample only at one timepoint. Lowering the cost of automated samplers, optimizing concentration methods, and aligning sampling methods across pathogens are all areas of focus. Thorough testing and standardization will be essential to ensure that the method chosen is suitable for pathogens of interest.

The prevalence of target pathogens varies geographically and so nimble, adaptable platforms are optimal for multi-pathogen detection, with customizable TaqMan array cards[9] and qPCR both demonstrated approaches. However, in some cases genomic sequence data will be required, making a targeted or metagenomic sequencing approach necessary. Direct detection, sequencing, and bioinformatics tools for environmental surveillance that are rapid, adaptable to newly emerging pathogens, cost-effective, and easily deployable also need to be developed.

Translating data from environmental surveillance into an assessment that is informative for public health action requires knowledge of the sensitivity and specificity of environmental surveillance, which are affected by the size of the catchment area and sample characteristics (including pH and temperature); but these are not consistently collected. Development of a minimal set of reporting criteria would support inference from environmental surveillance data and drive forward improvements in test accuracy, including limits of detection. Analytical frameworks to integrate information from environmental surveillance and clinical surveillance systems need to be developed. Dashboards developed during the SARS-CoV-2 pandemic are a useful way to rapidly and visually present data and to incorporate environmental surveillance data into national public health systems (as in Dhaka, Bangladesh: https://dhakaesforsars-cov-2.research.virginia.edu/), and these public facing tools should be developed further to support epidemiological inference. Action plans should be developed with stakeholders to articulate appropriate actions in response to the combined information from clinical and environmental surveillance data for each situation or setting [10]. Finally, quantification of the costs and benefits of multi-pathogen environmental surveillance are required to support decisions on how these investments should be prioritized. WHO-led review of information provided by environmental surveillance, and guidelines (as has been done for SARS-CoV-2: https://www.who.int/publications/i/item/WHO-HEP-ECH-WSH-2022.1 , and for polio: https://apps.who.int/iris/handle/10665/67854) on operationalizing environmental surveillance and interpreting data from these systems may be useful to aid broader implementation.

Sustainable environmental surveillance systems require reliable funding. Identifying funding for multi-pathogen environmental surveillance could be challenging in low-resource settings given constrained government budgets, a potential focus on global health security via a few sentinel systems, and single pathogen-specific funding mechanisms. We are encouraged by the promise of support for multi-pathogen environmental surveillance from the G7 group of nations (http://www.g7.utoronto.ca/healthmins/2022-0520-communique.html). We are also hopeful that networks across low- and high-resource settings where environmental surveillance is being undertaken could lead to shared tools and methodological approaches, ultimately lowering costs at scale for integrated, multi-pathogen surveillance in low-resource settings.

Environmental surveillance has clearly been demonstrated to be useful in polio and SARS-CoV-2, and is increasingly seen as a viable surveillance system for broader public health use. Methods need to be optimized across the range of environmental surveillance use-cases and pathogens. In addition, multiple strands of evidence are required to build the case for integrated, multi-pathogen, environmental surveillance system (Box 1). Funders, the WHO, nation states, industry partners and academics will need to coordinate their efforts in order to develop standardized approaches and guidelines for environmental surveillance, acknowledging the varied contexts of sanitation systems between high- and low-resource settings.

Box 1. A research and development agenda for environmental surveillance of infectious disease pathogens

Development of tools for sampling site selection in low-resource, non-sewered networks
Research to better understand how sampling frequency and methods may be aligned across pathogens
Adaptable, cost-effective direct detection, sequencing, and bioinformatics tools for priority pathogens
Minimal criteria for reporting environmental surveillance data
Validation of environmental surveillance for each pathogen by deployment in the field alongside hospital- or clinic-based surveillance that uses gold standard diagnostics
Development of frameworks to integrate environmental surveillance with clinic-based surveillance data
Examine the cost of population-based environmental surveillance, and build the case for sustained funding
Develop best practices for communicating environmental surveillance results to policy makers

Figure legend

Figure 1: Use cases may drive measurement goals and environmental surveillance system design. The goal of poliovirus surveillance is eradication; environmental surveillance, including genomics, is used to monitor spatial and temporal distributions of both wild type and vaccine-derived viruses, with any detection leading immediately to vaccination campaigns to prevent disease. SARS-CoV-2 environmental surveillance has been used to monitor trends and to control outbreaks by informing the use of non-pharmaceutical interventions; genomics has allowed detection of variants of concern, and the identification of novel variants. Environmental surveillance of vaccine-preventable diseases such as

Typhoid can provide information on transmission levels, and inform vaccine deployment, and allow monitoring of vaccine impact.

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Competing interests

The authors report no financial or non-financial conflicts of interest.

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