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Roadmap for Managing SARS-CoV-2 and Other Viruses in the Water Environment for Public Health

Gang Liu [a], Jiuhui Qu [a,*], Joan Rose [b], Gertjan Medema [b,c,d]

[a] Key Laboratory of Drinking Water Science and Technology, Research Centre for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China
[b] Department of Fisheries and Wildlife, Michigan State University, East Lansing, MI 48823, USA
[c] KWR Water Research Institute, Nieuwegein 3433 PE, Netherlands
[d] Sanitary Engineering, Department of Water Management, Faculty of Civil Engineering and Geosciences, Delft University of Technology, Delft 2628 CN, Netherlands

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ABSTRACT

The water sector needs to address viral-related public health issues, because water is a virus carrier, which not only spreads viruses (e.g., via drinking water), but also provides information about the circulation of viruses in the community (e.g., via sewage). It has been widely reported that waterborne viral pathogens are abundant, diverse, complex, and threatening the public health in both developed and developing countries. Meanwhile, there is great potential for viral monitoring that can indicate biosafety, treatment performance and community health. New developments in technology have been rising to meet the emerging challenges over the past decades. Under the current coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the world's attention is directed to the urgent need to tackle the most challenging public health issues related to waterborne viruses. Based on critical analysis of the water viral knowledge progresses and gaps, this article offers a roadmap for managing COVID-19 and other viruses in the water environments for ensuring public health.

1. Introduction

The field of virology was founded after Dmitri Ivanovsky described a non-bacterial pathogen infecting tobacco plants in 1892, and a few years later (1898) Martinus Beijerinck discovered the tobacco mosaic virus [1]. However, after more than a century, the identified and reported viruses are still far less than 1% of the total virome [2,3].

Viruses spread in many ways; humans' respiratory viruses can be transferred through coughing and sneezing, as seen with the "regular" influenza viruses and the on-going pandemic coronavirus disease 2019 (COVID-19) that moved quickly through over 185 countries and has infected more than 31.6 million people (till 23 September 2020) [4,5]. Contact with contaminated fomites and hands are also important exposure pathways for these viruses. For enteric viruses, ingestion of contaminated water or inhalation of aerosol is an important transmission pathway, and well documented [6].

There has been a consensus that virus concentrations in water are low and difficult to detect. Yet, the use of meta-viromics technologies led to the discovery that water viruses are not only abundant (up to 10^{11}–10^{13} L^{-1}) [7], but also diverse [3,8]. A key question, then, is whether the many viruses present in water and particularly in wastewater, including the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of the on-going COVID-19 pandemic, are viable and infectious. One of the key potential benefits of monitoring is the valuable insight it may offer on the circulation of viruses and the scale of future outbreaks [9]. Based on critical analysis of progresses and gaps in the water viral knowledge, this article offers a roadmap for managing COVID-19 and other viruses in the water environments for ensuring public health, with focuses on the problems, potentials, and perspectives.

2. Problems

2.1. Waterborne diseases

Viruses in water can disseminate through water environments affecting downstream human, animal, and plant health [10]. Most

* Corresponding author.
E-mail address: jhqu@rcees.ac.cn (J. Qu).

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viruses are highly host specific and mainly the human enteric viruses pose the greatest health concerns for waterborne transmission. Generally, the enteric viruses are small (size of nanometers) and quite potent (with an 50% infectious dose (ID50) of just a few to 10^3 viral particles[†]) [11,12]. These particles are typically shed by infected persons over long periods of time and in high concentrations, have a lengthy survival time and have high disinfection resistance in water environments [13]. These characteristics allow many enteric viruses to bypass conventional water treatment processes and play a significant role in water-related outbreaks of viral diseases [14]. Actually, there are other viruses with less epidemiologic importance but are also capable of waterborne transmission, such as the human reovirus, parvovirus, parechovirus, polyomavirus, torovirus and coronavirus [15].

Since the first isolation of enteroviruses in 1941, more than 140 enteric viruses have been detected in water environments, the list of which continues to grow every year [16–18]. Until recently, more than 40% of diarrhea cases in the United States were caused by unknown agents, which many believe were undiagnosed or undiscovered viruses [19]. The World Health Organization (WHO) has classified viral pathogens that have moderate to high health significance including the adenovirus, astrovirus, hepatitis A and E viruses, rotavirus, norovirus, enteroviruses, and other caliciviruses, which are commonly associated with gastroenteritis, causing diarrhea, abdominal cramping, vomiting, and fever [20]. Those viruses can cause more serious illnesses (e.g., chronic diarrhea, liver disease, or neuro-invasive disease) for pregnant women, young children, the elderly and immune-compromised people [21].

For example, the diarrhea caused by the rotavirus contributed to 1.2 million deaths of young children in 2012 [22,23]. Developing countries suffer most of the disease burden because of their lack of sanitation and access to safe water, widespread malnutrition and large populations of human immunodeficiency virus (HIV)-positive people [21]. Meanwhile, developed countries have also been experiencing outbreaks, such as the norovirus in the United States, France, Japan, Sweden, Switzerland, the United Kingdom, and the Netherlands [24].

2.2. Assessment strategies

2.2.1. Viromics and detection

It is important to measure viruses in aquatic environments as a way to demonstrate the efficient control of viruses. One of the major efforts over the past decades has been devoted to the study of viruses using cultivation in tissue cultures, immunofluorescence, radioimmunofocus assay to nucleic acid probes, copy DNA (cDNA) probes, polymerase chain reaction (PCR), reverse transcription (RT)-PCR, (multiplex) quantitative polymerase chain reaction (qPCR), and microfluidic qPCR [8,17,25]. Today, the use of next generation sequencing and shotgun metagenomic sequencing has revolutionized and expanded the horizon of the viral studies in water, such that viruses can be detected quickly and accurately [3,26,27]. However, the potential for increasing knowledge of the water virome using metaviromics is on the brink of tremendous growth in the coming years; applications of raw sequencing quality and downstream bioinformatics deserve particular attention. The upstream steps such as virus concentration and DNA/RNA extraction also need harmonizing for cross comparison of results and optimization to guarantee high quality shotgun sequencing.

2.2.2. Viral indicators

It is difficult and costly to measure infectious viruses one by one, which is hampered also by the lack of well-established viral indicators, the limited application of genomics-based multiplex quantitative methodology for viral detection and yet establishment of a global network of environmental virology laboratories. As a result, the biosafety of water systems worldwide is still being tested by measuring fecal indicator bacteria (mainly *Escherichia coli* (*E. coli*)) using 100-year-old technology [28], though it is well known that bacterial indicators do not represent the occurrence and removal/inactivation of viruses in water systems [29].

Efforts have been made to use bacteriophages as surrogates of viral pathogens because they are more representative than fecal indicator bacteria regarding the shedding by hosts, the diffusion routes in environments and morphological characteristics, such as female (F)-specific RNA coliphages MS2 that can infect *E. coli* [30]. Other examples include the plant pathogen pepper mild-mottle virus (PMMoV) and cross-assembly phage (crAssphage), both of which are highly abundant in human fecal samples (PMMoV, 10^5–10^{10} gene copies per liter; crAssphage > 10^{10} gene copies per liter [31–33]. However, the behavior of phages in a water environment and their responses to water treatment are different from human viruses [34,35].

Now, meta-viromics is shedding new light on the importance of having proper viral indicators. Studies on untreated sewage found 0.4×10^{13}–1.5×10^{13} virus particles per liter [2,7] with immense diversity, including viruses associated with numerous bacteria, archaea, and unicellular eukaryotes [36,37]. Wastewater provides an opportunity to sample the viral diversity infecting cellular organisms from all kingdoms of life [2] and select viruses that are abundantly and ubiquitously present in human sewage, in much higher numbers than human viruses and the coliphages that have been used traditionally. Successful selection of indigenous viruses will avoid the common over- or under-estimation of water system virus safety related to using external indicators [38,39]. The critical scientific challenge is to find indigenous viruses that react similarly as waterborne viruses do to different treatments.

2.2.3. Management

Sanitation is important for managing waterborne viruses because feces contain an abundance of viral pathogens that can deteriorate surface water quality and infect people [40]; this is especially true for the rural area and developing regions. As simulated by Hofstra's group [41,42], total viral emissions to surface water were 2×10^{18} in 2010, which were becoming worse due to increased populations and climate changes [43]. Wastewater and water treatment processes can be good barriers for ensuring the viral safety of water environments, especially for water reuse, recreation, and drinking. For virus removal by wastewater treatments, Amarasiri et al. [44] compared and summarized that the virus log removal value (LRV; e.g., if 90% was removed, LRV = 1; and if 99% was removed, LRV = 2) of membrane bioreactor, conventional activated sludge, microfiltration, ultrafiltration, constructed wetlands and ponds are 1.5, 2.0, 1.4, 3.7, 0.9, and 2.3, respectively.

Given the increasing trend of wastewater reuse due to population growth, urbanization and droughts, especially indirect potable reuse, there is a strict requirement for viruses of LRV $\geq$ 12 [45,46]. Regarding drinking water treatments, the LRV of conventional treatments, ultrafiltration, disinfection with ozonation or chlorination, ultraviolet (UV), and reverse osmosis (RO) is 1.7–2.4, 3–4, 4–5, 3.0–6.4, and > 7, respectively [38,47–49].

Typically, the LRV is tested with selected model viruses (e.g., MS2 and PMMoV) [50,51]. However, the LRV can be variable for different viruses [47]; the mechanism for virus removal is not yet clear, which has hampered the effective treatment of viral pollution. Despite the treatments that have been applied and regardless of the developing stages of the countries, there is a wide range of viral pathogen occurrence in treated drinking water around the

[†] http://qmrawiki.org/framework/dose–response.

world [14], such as the United States [52], Republic of Korea [53], South Africa [54], Spain [55], New Zealand [56], and China [57]; no need to list countries with known poor sanitation facilities.

3. Potentials

3.1. Viral regulations in reclaimed water and drinking water

If the treated wastewater will be reclaimed, virus removal is required and regulated to a performance target [58,59]. In the United States, for both indirect potable reuse (IPR) and direct potable reuse (DPR), an LRV of 12 and 8 are required when using untreated wastewater and wastewater treatment plant effluent, respectively, as a source [46,60]. In Queensland, Australia, achieving an LRV of 6.5 in wastewater treatment can be classified as the highest quality reclaimed water, while an LRV of 9.5 is required for drinking purposes [61]. However, recent studies found that the threshold of LRV = 12 failed to meet the benchmark of 1 infection per 10 000 people per year and another additional 2–3 LRV will be necessary [62].

For drinking water, efforts have also been made to develop viral regulations worldwide, such as in Australia [63], the United States [64], and the Netherlands [65]. For Australia, there are no regulated values for enteric viruses. Instead, coliphages targeting *E. coli* are used. The US drinking water regulations are performance-based standards requiring enteric virus removal/inactivation of 99.99%, but specific virus families are not individually regulated. The appropriate disinfectant dose and its residuals must be maintained for microbiological water quality regulations. In the Netherlands, drinking water is distributed without chlorine or any disinfectant residuals; water utilities must conduct quantitative microbial risk assessment (QMRA) every four years to address infection by enterovirus with a threshold of one infection per 10 000 persons per year.

For both reclaimed water and drinking water, it will be highly necessary to have both general LRV and proper viral indicators regulated to assess the viral safety of the water systems. For ensuring water safety, when scanning viral parameters and evaluating the viral safety, it is essential to consider the variable performances of different viruses regarding their survival time, resistance to environmental pressure and infection risks.

3.2. Indigenous natural viruses as treatment performance indicators

To evaluate whether water treatments can efficiently remove viruses, it is important to monitor the performance with or without contamination from viral pathogens. Taking nanofiltration (NF) and RO as examples, it is critically important to have operational monitoring of membrane integrity, especially for water reuse or for drinking water purposes, because minor breakthroughs of pathogenic viruses may result in serious human health risks [38]. However, direct routine measurement of viral pathogens is impossible because their extra low concentrations in both source and treated water. It was proved that the natural viruses present in source water can be better indicators than the conventionally used membrane-integrity test either by total organic carbon (TOC) and turbidity [66,67], or by viral surrogates MS2 [38]. After mapping the viruses in source water, indigenous natural viruses with concentrations > 10^8 gene copies per liter were selected, which demonstrated RO integrity by showing an LRV > 7. The same protocol can be applied to monitor the performance of other treatments and evaluate if the treatment is virus tight, which is: mapping natural viruses in source water, selecting high abundance viruses which can represent typical pathogenic viruses as performance indicators, and testing the performance by calculating LRVs.

3.3. Sewage surveillance of viruses to support public health surveillance

Human viruses are excreted at high concentrations in the feces of infected individuals with or without symptoms, such as ~10^{11} virus particles per gram of feces for noroviruses and adenoviruses [8] and 10^8 gene copies per gram of feces for the current COVID-19 virus in about half of the cases [68,69]. For this reason, monitoring the target viruses in sewage can be used to reflect human infections and virus circulation. A good example is sewage surveillance for poliovirus (PoV), which has been included by WHO in the strategic plan of the global polio eradication initiative supplementing acute flaccid paralysis surveillance [70]. For the outbreaks in Finland [71], Israel [72], and the Netherlands [73], by monitoring PoV in the sewage, the researchers were able to indicate wide geographical circulation of the virus in the country, detect epidemic virus in areas without reported paralyzed cases and/or a few weeks before the first case of poliomyelitis was reported, demonstrated the great potential power of monitoring target viruses in sewage to herald epidemics and investigate outbreaks [74].

For the on-going pandemic COVID-19, Medema et al. [75] started monitoring COVID-19 virus RNA in sewage in February 2020 before COVID-19 cases were detected in the Netherlands. Their results turned from all negative in February into five and six out of the seven sampled wastewater treatment plants (WWTPs) positive in early and middle March 2020. Remarkably, they detected COVID-19 in the city of Amersfoort six days before the first cases were reported, indicating again that monitoring the target virus in sewage can be a valuable means of measuring the circulation of a virus in the community and sending early signals for taking timely actions. For the current situation worldwide, many countries are short of testing consumables and mild cases are not being reported or tested, so measuring COVID-19 in sewage could be a good and necessary complement.

Countries in Asia, Europe, and in America are facing different stages and conditions as they fight the pandemic. Monitoring sewage could serve as early warning for yet unaffected region, indicate virus circulation and infections for the expanding region with or without sufficient test kits, and early warning for the cities finishing lockdown to identify re-emergence of the virus in the community. The last one is of great importance for the cities and countries, who have devoted extraordinary efforts controlling the virus and are now facing high pressure to recover their economies. An important challenge is to identify those persons who are infected but are without symptoms in order to reduce risks before re-opening societal activities. It is possible that by combining the monitoring of the sewage at treatment plants, sewage collection mains and the major drainage pipe connection points, one could track the hot zones of infected patients and neighborhoods and, thus, ultimately prevent further spread of the virus in a timely manner.

To use virus levels in sewage as a public health surveillance tool during pandemics, it is critical to conduct clinical investigations on levels and distributions in fecal excretions for infected cases and recovered patients and the time of excretion. Ultimately, it will be valuable to have a quantifiable correlation between the detected viral gene copies and the number of infections.

4. Conclusions

For assessing the viral risks and ensuring the biosafety of a water environment, we would like to conclude this article with the following perspectives as roadmap on urgently needed global actions that should be taken (Fig. 1).

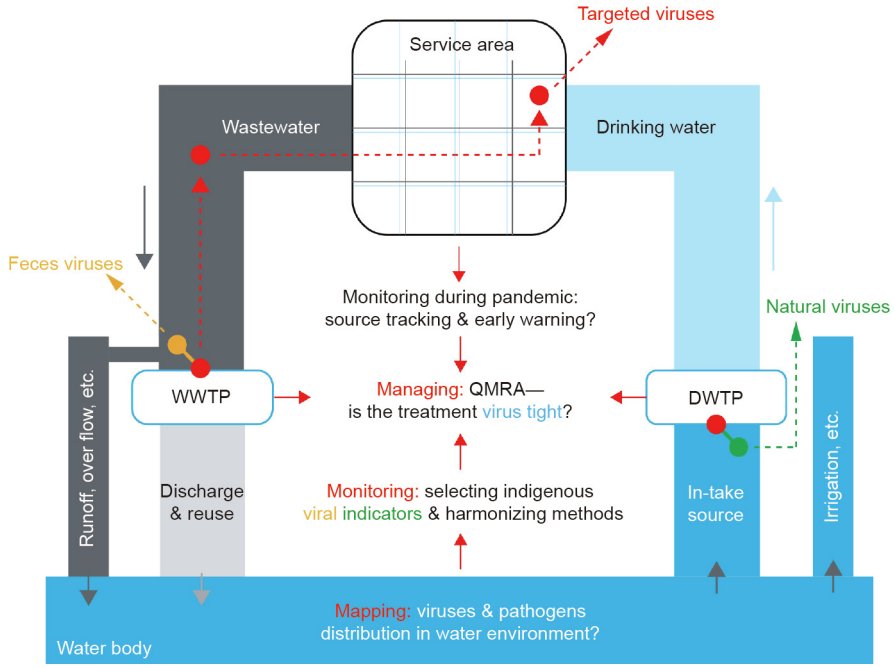

Fig. 1. Overview of the pathways of viruses in water and the urgent questions to be addressed regarding mapping, monitoring, and managing viruses in water environments. WWTP: wastewater treatment plant; DWTP: drinking water treatment plant.

(1) Mapping water viruses. Following the example set by the Global Water Pathogen Project (GWPP[†]), it is urgently necessary to expand our understanding of the sources, fate, and transport of viral pathogens as well as other pathogens in our water systems. Mapping the water viruses using up-to-date meta-viromics is essential to reveal the temporal-spatial distribution of water viruses, construct national and international water viral databases, and advise about efficient management strategies.

(2) Selecting viral indicators. Viral indicators are definitely needed for the regular monitoring of water environment biosafety, especially because indicators like *E. coli* fail to sufficiently indicate the viral risks while requiring significant human effort and resources worldwide. Based on the scanning of water environments, it is important to select proper indigenous viruses from human sewage as viral indicators for viral pathogens, and from source water as viral indicators for treatment performances.

(3) Harmonizing test protocols. Different testing protocols make it difficult to have good comparisons case-by-case, which is hampering researchers from joining their efforts. It is necessary to find the best protocols and principals of good sampling/methodology while allowing for advances in pre-treatment steps through data processing including concentration, DNA/RNA extractions, reverse transcription, qPCR, sequencing, and bioinformatics, which can avoid variable detection efficiencies during and favor the international unified work force.

(4) Assessing viral risks. Assessing the risks is the beginning of the understanding necessary for management. Though the QMRA method is well established and has been successfully applied for years, the Netherlands is still the only country having a formal QMRA that has been included in their drinking water regulations. For a systematic risk evaluation, this method is highly recommended to be introduced and promoted widely, especially in regions where water pathogens have not gained enough attention.

(5) Setting a monitoring framework. Aiming for a strong sewage monitoring program during pandemics, it is necessary to set up a standard action framework to complement the clinical tests and support public surveillance during different stages of the pandemic's development. First, making clear the virus's presence, survival, and shedding characteristics in sewage, then concluding with knowledge of the risk of the virus's spread and infection via water. This should become part of any public health strategy which is based on the monitoring results, evaluation of virus's circulation, tracking the original areas of the infected patients, if possible, and finally, advising the government on timely management strategies. Furthermore, establishing such a framework will also be valuable for other disease and human parameters, such as anti-microbial resistance, the use of pharmaceuticals, illicit drugs, and so forth.

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Compliance with ethics guidelines

Gang Liu, Jiuhui Qu, Joan Rose, and Gertjan Medema declare that they have no conflict of interest or financial conflicts to disclose.

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