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Review

Wastewater surveillance for population-wide Covid-19: The present and future



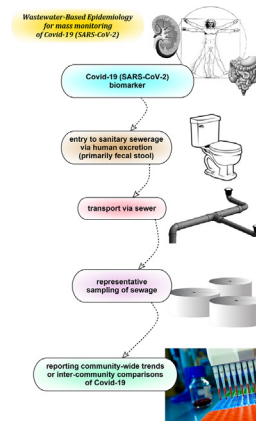
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HIGHLIGHTS

- Wastewater-based epidemiology (WBE) could play critical roles in the Covid-19 pandemic.
- WBE can help solve the pressing problem of insufficient clinical diagnostic testing.
- It could serve to better target and direct the application of diagnostic testing.
- It could help reduce countless domino effects from the pandemic.
- WBE might be the only means for providing rapid, inexpensive mass surveys.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:

Received 26 April 2020

Received in revised form 20 May 2020

Accepted 20 May 2020

Available online 23 May 2020

Editor: Dr. Damia Barcelo

Keywords:

Wastewater-based epidemiology (WBE)

Sewage

Covid-19

SARSCoV-2

Pandemic

Epidemiology

ABSTRACT

The Covid-19 pandemic (Coronavirus disease 2019) continues to expose countless unanticipated problems at all levels of the world's complex, interconnected society – global domino effects involving public health and safety, accessible health care, food security, stability of economies and financial institutions, and even the viability of democracies. These problems pose immense challenges that can voraciously consume human and capital resources. Tracking the initiation, spread, and changing trends of Covid-19 at population-wide scales is one of the most daunting challenges, especially the urgent need to map the distribution and magnitude of Covid-19 in near real-time. Other than pre-exposure prophylaxis or therapeutic treatments, the most important tool is the ability to quickly identify infected individuals. The mainstay approach for epidemics has long involved the large-scale application of diagnostic testing at the individual case level. However, this approach faces overwhelming challenges in providing fast surveys of large populations.

An epidemiological tool developed and refined by environmental scientists over the last 20 years (Wastewater-Based Epidemiology – WBE) holds the potential as a key tool in containing and mitigating Covid-19 outbreaks while also minimizing domino effects such as unnecessarily long stay-at-home policies that stress humans and economies alike. WBE measures chemical signatures in sewage, such as fragment biomarkers from the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), simply by applying the type of clinical diagnostic testing (designed for individuals) to the collective signature of entire communities. As such, it could rapidly establish the presence of Covid-19 infections across an entire community. Surprisingly, this tool has not been widely embraced by epidemiologists or public health officials. Presented is an overview of why and how governments

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should exercise prudence and begin evaluating WBE and coordinating development of a standardized WBE methodology – one that could be deployed within nationalized monitoring networks to provide intercomparable data across nations.

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Contents

1. Introduction	2
2. WBE for mass surveillance of Covid-19	3
3. What R&D is needed to advance WBE as a valuable public health tool?	4
4. The risks posed by insufficient monitoring data	5
5. National involvement and coordination of WBE R&D across nations	6
Declaration of competing interests	7
Acknowledgment	7
References	7

1. Introduction

The focus of this paper involves “Coronavirus disease 2019” (known as Covid-19), which is caused by an infectious virus, “Severe Acute Respiratory Syndrome Coronavirus 2” (known as SARS-CoV-2). The first published studies of what would become a pandemic began to be published in late January 2020, when the novel corona virus was known as 2019-nCoV (Chan et al., 2020; Huang et al., 2020).

During the Covid-19 pandemic, countless unexpected realities have been revealed. Hidden, cascading domino effects have proved most challenging to prevent – ever lurking in the shadows of complex chains of an interconnected world. Probably the most exasperating has been the emerging realization that the health, safety, and economic well-being of humans, the functioning of healthcare, food security, the stability of economies and financial institutions, and the viability of democracies might all rely on the widespread availability of fast analytical test methods for certain biomolecules.

Other than effective prophylaxis or therapeutic cures, few things are more important in a pandemic than knowing who is infected (and infectious). In a matter of months after SARS-CoV-2 infections spread worldwide, most governments struggled with trying to quickly determine the most fundamental aspect of the pandemic – the distribution and magnitude of infected populations. This problem was greatly exacerbated by the fact that facile transmission of the virus could be accomplished via the air and that a major vector of transmission was always concealed as an unknown portion of the asymptomatic general population. This greatly increased the difficulty in efficiently directing the public health resources essential for the containment, control, or mitigation of transmission. Moreover, possibly the most successful approach is total suppression (Casella, 2020), which requires an especially early warning.

A second urgent need quickly followed. Without the ability to rapidly and inexpensively monitor randomly selected individuals for infectious virus (e.g., via molecular nucleic acid tests) or evidence of prior exposure (via antibody tests), the ability to quickly isolate or quarantine contagious individuals simply did not exist. The only option was simplistic and involved indiscriminate isolation (city-wide stay-at-home, shutdown, or lock-down policies) and physical distancing practices for entire populations – to discourage the congregation of people beyond those they live with.

This in turn handcuffed governments from making informed decisions critical for knowing how or when large portions of the population could return to their workplaces (the quandary of balancing lives and livelihoods). Re-engaging businesses with the economy would rely too much on guesswork and luck – and far too much effort to rationally coordinate beyond geographic and political boundaries. Such was the

reality that emerged in many countries during the first months of 2020 because of the Covid-19 pandemic.

Not unexpectedly, the dominoes began to fall with the disruption or collapse of countless manufacturing supply chains and large sectors of economies – in turn jeopardizing the functioning of financial institutions and investment markets. At the same time, certain activities necessitating mass gatherings were essential to the maintenance functions of societies (e.g., food chains and essential public health services), continuing to pose heightened risks for all. In democracies, in-person poll-voting became a quagmire for logistics and debate. Civil unrest, discord, and instability can become an inevitable societal risk because of the many who are unable to support their families by remaining isolated. The possibilities are endless and potentially catastrophic. Just consider the vulnerability of power grids as one example (Smith, 2020).

Much still remains to unfold with the domino, knock-on effects of this pandemic. Moreover, even if the world can figure out how to efficiently deal with Covid-19, more pandemics are inevitably looming – some inevitably amplified yet further by coinciding natural disasters (e.g., see Smith, 2020).

With this brief thumbnail sketch of the world’s current quagmire, this paper discusses the potentially key role that environmental science could play in solving some of the many obstacles and challenges currently faced in monitoring the spread of Covid-19. The existing tools were designed specifically for diagnostic (or serological) testing of individuals. Scaling these conventional tests for mass surveillance of populations is fraught with tremendous challenges, including the extremely high costs for repeatedly testing large portions of population (Allen et al., 2020), involving enormous human resources, insufficient sensitivity, and inadequate throughput; note, however, there are ways to greatly improve sensitivity – especially when the incidence of negatives will be high (e.g., in infected asymptomatic populations) (Suo et al., 2020) – and to increase the throughput of conventional methods (NAS, 2020), such as via pooled sampling (group testing) (see: Bergel, 2020; Deckert et al., 2020; Shani-Narkiss et al., 2020; Sinnott-Armstrong et al., 2020).

Over the last 20 years, environmental scientists continue to develop an armamentarium of monitoring and epidemiological tools capable of measuring the combined, collective activities or health status of entire populations. This approach is analogous to conventional diagnostic urinalysis performed en masse but instead targets sewage (Daughton, 2020a; Sims and Kasprzyk-Hordern, 2020). Designed to quantify the community-wide usage of a wide expanse of chemicals (originally illicit drugs), this methodology (Wastewater-Based Epidemiology – WBE) is now beginning to be applied to Covid-19 (see: Ahmed et al., 2020; Bar Or et al., 2020; La Rosa et al., 2020; Medema et al., 2020; Nemudryi

et al., 2020; Randazzo et al., 2020a, 2020b; Wu et al., 2020b; Wurtzer et al., 2020). However, the numbers of research projects and pilot studies currently planned or in progress globally far exceed these and are rapidly growing. Three current review articles discuss many of the complex issues surrounding the application of WBE to infectious disease tracking – Covid-19 in particular (Kitajima et al., 2020; Sims and Kasprzyk-Hordern, 2020; and Xagorarakis and O'Brien, 2020). A theoretical assessment of WBE's feasibility and cost in monitoring for Covid-19 at scale is presented by Hart and Halden (2020).

2. WBE for mass surveillance of Covid-19

The most adverse domino effects from an epidemic can be reduced or minimized only by implementing sufficient, timely, targeted testing. But what is considered sufficient testing? Testing during epidemics has always been impaired by the lack of any option other than application of tests designed for clinical detection and diagnosis of current infections (or serological tests for establishing past infections, e.g., Gronvall et al., 2020). Most importantly, this approach to testing needs to continually increase test coverage (i.e., the percentage of the population tested) until a key level is achieved. This level is the number of tests that must be completed in order to reveal a single positive (confirmed) case. This ratio is the most direct indicator of the extent of infection in the general population (Hasell et al., 2020). A low ratio (when using random sampling) points to a high incidence of infection and therefore the need for more intensive testing until the ratio significantly increases (where ever-increasing amounts of testing are required to confirm each additional case of infection). This indicates increasing success in containment or mitigation measures.

Nevertheless, diagnostic tests were never intended for mass surveillance. These tests are not only time-consuming and costly, but they can pose serious exposure risks for those who administer the tests. They were never intended for massive scales. There are two basic alternatives to solving this problem: (1) dramatically increase the throughput of the conventional diagnostic tests, and/or (2) minimize the number of tests required to reveal each positive case.

The first can be partly accomplished with the use of more advanced versions of current diagnostic tests (NAS, 2020), such as pooled-sample analysis (e.g., Deckert et al., 2020). Pooled-sample analysis could greatly increase testing capacity and throughput, especially for PCR-based methods (nucleic acid-based polymerase chain reaction); although not as sensitive as PCR testing, antigen testing (e.g., capsid proteins) is just emerging for SARS-CoV-2, with the US FDA's emergency use authorization for the first antigen test (US FDA, 2020). The second can be accomplished by pre-targeting sub-populations that have a higher probability of infection. This would conserve the use of available diagnostic tests.

Metaphors likening the control of Covid-19 to war can be useful. As such, WBE's role in fighting the spread of Covid-19 would be analogous to warfare where "forward observers" are used to improve the outcomes of artillery fire by greatly improving the accuracy of targeting. WBE would, in effect, provide a call warning for fire (i.e., "start diagnostic testing here"), directing fire, adjusting fire, and confirming mission accomplished. This would greatly reduce the demand for diagnostic testing and also reduce supply-chain shortages caused by insufficient manufacturing capacity. The metric of success for WBE when used for targeting the use of clinical diagnostic testing would be lower ratios for "Tests Administered" per "Case Confirmed" (counter intuitively, maximize the positivity test rate).

The application of WBE can be extended beyond its current confines that were imposed by privacy, ethics, and legal concerns – boundaries recognized in WBE's pre-existing applications for illicit drug monitoring (Prichard et al., 2014, 2017). Its utility for targeting where diagnostic testing should be directed could be amplified by monitoring smaller, key, confined sub-populations. Major targets to monitor would include the following (some of which have already proved problematic by

promoting outbreaks): schools, universities (e.g., dormitories), congested public housing (where new cases can be easily overlooked and outbreak clusters can quickly emerge), hospitals, long-term care facilities, prisons, manufacturing and warehouse facilities, meat processors, maritime ships, naval vessels (e.g., Werner, 2020), airports and airlines, mass entertainment venues (arenas, stadiums, and concert halls), indoor exercise facilities, and shopping malls, among other confined areas. Of particular interest would also be sub-populations under-served by healthcare – whether because adequate healthcare is not available or because certain individuals actively avoid seeking health care (De Filippo et al., 2020). At the same time, WBE would also be useful for assuring when a facility might be virus-free; this, however, would rely on method detection limits that are reliably low.

The reality is that massive-scale diagnostic-based testing is simply not possible in most countries given the enormous costs and current limitations of manufacturing and supply-chains. Testing must get smarter and better targeted. This is where WBE becomes so important. By avoiding the testing of populations likely to be negative, WBE would serve to magnify the value of diagnostics testing by "making them count". One of the biggest challenges for many countries, regions, states, and cities is the formulation of a data-driven strategy for guiding when to "re-open" economies and when they might need to re-close during resurgence (Allen et al., 2020; Redlener and Fair, 2020). WBE could play a key role in optimizing these decisions by providing the earliest possible dates for: (1) beginning the post-isolation phase (when businesses could restart and population isolation could be terminated) and (2) reinstatement of population-wide isolation upon Covid-19 rebound or seasonal re-emergence. This early-warning ability minimizes the major dual problems of re-opening too soon or isolating too late, both of which could set back public trust even further and cause yet more damage to economies. By establishing baselines for the incidence of Covid-19 before re-opening, both resurgence and acceleration could be readily detected.

One of the more important potential advantages of WBE over diagnostic testing would be an ability to detect Covid-19 before it might be possible with surveillance using random diagnostic testing. This would partly rely on the timing of virus shedding via the stool with respect to the initiation of infection or the onset of signs and symptoms (if any). But it is not yet clear if any generalizations will ever be possible. The time at which RNA from SARS-CoV-2 becomes PCR-detectable from shedding into stool can vary widely (and not even occur in all cases) – within one or several days of symptom onset and persisting for a month or so beyond the resolution of signs and symptoms – even for children (Cai et al., 2020; Chen et al., 2020b; Holshue et al., 2020; Lo et al., 2020; Wölfel et al., 2020; Wu et al., 2020a; Xing et al., 2020; Zhang et al., 2020a). Shedding via the stool can also persist after pharyngeal samples test negative (Chen et al., 2020a). Fecal shedding studies for presymptomatic cases (Gandhi et al., 2020) would be very important for WBE, but the existing data are very sparse. On a related issue, although some case studies have verified the presence of viable (infective) virions in feces (Wang et al., 2020; Xiao et al., 2020), others report the failure to recover infectious particles (Wölfel et al., 2020). Nonetheless, caution is advised regarding occupational exposure and in sampling sewage (WHO, 2020a).

As an aside, an important point merits some consideration. There is no reason that WBE must be based on the same analytical platforms used in clinical diagnostic testing (i.e., direct measures of viral infection such as PCR or antigen testing). WBE for Covid-19 (or diseases caused by any other infectious agent) need not be limited to the monitoring of the actual infectious agent's nucleic acid or an antigen. WBE's usefulness could be greatly expanded by targeting endogenous biomarkers that are significantly elevated in the diseased state. Benefits of targeting indirect markers of infection might include reduced analytical costs and broader availability (e.g., by use of immunoassays) or serving as better leading indicators of infection (providing the possibility of earlier alerts); biomarkers that are excreted extensively in urine (as opposed

to feces), for example, would simplify sewage sampling and sample preparation prior to analysis. A likely place to start evaluating the use of biomarkers would be to make use of the fact that Covid-19 can involve extensive inflammatory damage. The archetype biomarker for systemic oxidative stress is the prostaglandin-like class of substances called isoprostanes (Daughton, 2012a; O'Brien et al., 2019); a range of other potential biomarkers (e.g., see: Daughton, 2018; Rice and Kasprzyk-Hordern, 2019) might also be excreted at elevated levels with Covid-19. Testing for biomarkers might have several other major advantages over the use of PCR: (i) biomarkers might be more universally excreted among infected individuals, (ii) excreted levels might better track the severity of infection, (iii) biomarker testing might have tighter ranges for per-capita excretion, facilitating better calibration and more accurate estimations of the number of infected individuals in a community, and (iv) avoiding a potential under-appreciated problem with using PCR, where RNA fragments may not be originating from viable virus, but rather from virus remnants (litter) from cleared infections and therefore could be overestimating the incidence or intensity of existing infections. This could well be a cause of repeated reports of recovered patients again testing positive for Covid-19 (e.g., Cha and Smith, 2020).

WBE could provide early warnings for community-wide emergence, resurgence (Kissler et al., 2020), status and trends (sustained transmission or amplification of transmission – acceleration or deceleration), suppression, subsidence, and elimination of Covid-19 or any other infectious disease. Deceleration could result from successful control measures or attainment of herd immunity. Should SARS-CoV-2 eventually become endemic (Galanti and Shaman, 2020), it could be critical to have an ongoing community-wide surveillance system to detect newly emerging clusters.

With a nationwide system of community WBE monitoring, maps could be readily generated showing patterns of clusters or areas where Covid-19 has yet to spread or where it has subsided. Infection densities could reveal community vulnerabilities or susceptibilities as a function of race, ethnicity, socioeconomic status, occupation, age structure, and climate, among others.

Note that since WBE has the ability to detect Covid-19 days before random diagnostic testing of asymptomatic individuals, it could save critical days in facilitating a head-start for contact tracing (e.g., Allen et al., 2020; Watson et al., 2020) because follow-up diagnostic testing can be better targeted to locate the infected individual(s). It would therefore have the potential to short-circuit significant forward transmission.

WBE could play an integral role in minimizing the occurrence of surges of serious cases whose numbers can overwhelm critical care hospital capacities and long-term care facilities. Preventing hospital surges is also critically important for minimizing a “collateral pandemic” (Galarza and Gazzeri, 2020). There could be untold numbers of non-Covid-19 cases who die prematurely, or unnecessarily, or with untimely/inadequate care – all indirectly because of Covid-19. Once critical care capacity is exceeded by Covid-19 patients, this serves to amplify deaths and morbidities for those who did not receive care simply because they were non-Covid-19 patients. This includes those who refuse or delay in seeking medical attention because of fear of contracting Covid-19, those who must wait too long to receive care, and those who had to be diverted to facilities incapable of providing sufficient care. Any action that can reduce hospital surges (such as “flattening the curve” of infection transmission) will reduce overall deaths. Early warnings are therefore critical.

Also worth emphasizing is that WBE might be the only means of indirectly inferring the portion of the total population that remains uninfected at any moment in time. In effect, this information serves to complement diagnostic testing (and syndromic surveillance) and to more fully construct the so-called surveillance pyramid. Likewise, it could provide better perspective on how well the results of diagnostic testing are reflecting the status of the general population. It also might

be the best way to convince a doubting public when infections are indeed spreading (but not yet reflected in hospital statistics) and whether the spreading has entered an acceleration phase. Of great importance, near-real-time community-wide monitoring could greatly increase community connectedness and sense of purpose, thereby improving willingness to comply with government recommendations for distancing and self-isolation. Importantly, and contrarily, WBE could reveal that suppositions regarding infectivity and spreading may have been overestimated (see contrarian views: Ioannidis, 2020; Roth et al., 2020). The importance of listening to contrarian views is discussed by Prasad and Flier (2020). WBE could play a key role in resolving scientific debates.

Also note that WBE could be used as a tool to guide the final phase of eradication (e.g., see: Brouwer et al., 2018). Once eradication efforts succeed to the point where severe cases are rare, but asymptomatic infections persist, WBE could prove to be very useful in surveillance of any newly emerging clusters that would otherwise escape detection.

Finally worth considering is whether WBE has the potential to generate a wealth of metadata related to the impact of Covid-19 at the community level. For example, WBE might be useful in testing or corroborating hypotheses involving the correlation of various community-wide population demographics with the magnitude and duration of SARS-CoV-2 measurements to probe inter-community disparities such as race, culture, income, healthcare availability, and occupation. WBE data could also be examined for correlations with drug manufacturer geographic prescribing data – notably for drugs suspected of improving or exacerbating Covid-19 therapeutic outcomes (Daughton, 2020b).

3. What R&D is needed to advance WBE as a valuable public health tool?

Past advancements in WBE have primarily relied on environmental scientists and analytical chemists, as the targeted analytes of interest had generally been anthropogenic, synthetic chemicals (Daughton, 2018). To expand the usefulness of WBE to infectious diseases and biomolecules, a much broader range of science disciplines will be required, in larger collaborations. Evidence that this is already happening can be seen with more involvement of microbiology (e.g., Wigginton and Boehm, 2020).

Sewage monitoring had already been established as a tool to detect existing threats from pathogens, particularly for polio virus (Anis et al., 2013; Berchenko et al., 2017; Brouwer et al., 2018; WHO, 2003). And within a few short months after the emergence of Covid-19, the first pilot studies began to appear for WBE's possible use as a tool for tracking Covid-19 (e.g., Ahmed et al., 2020; Bar Or et al., 2020; La Rosa et al., 2020; Medema et al., 2020; Nemudryi et al., 2020; Randazzo et al., 2020a, 2020b; Wu et al., 2020b; Wurtzer et al., 2020). However, much more research will be required for its full development.

The attractiveness of WBE has always resided in its conceptual simplicity. However, resolution of some complex, underlying technical details could stymie its full potential value as a widely adopted monitoring approach for community-wide health and disease. For Covid-19, one of the most important details is signal calibration – what do the data actually mean? The biggest unknown surrounds the need to calibrate the targeted marker for Covid-19 (which currently is primarily viral RNA) against the actual number of cases the signal actually represents. But as already mentioned, this problem might be more easily solved by targeting key endogenous biomarkers instead.

There are three basic forms that WBE could theoretically embody. Each would require increasingly more research to develop, calibrate, and validate:

(1) **Qualitative approach** that merely indicates whether a certain minimum level of infection is present – a binary yes/no depending on the sensitivity (limit of detection) of the analytical method used for

detection (e.g., rt-PCR versus antigen). The limited research published to date is focused on this embodiment.

(2) **Semi-quantitative approach** capable of indicating *relative* levels of infection. This form would be capable of revealing acceleration or deceleration phases of infection, but only within an individual community (not across communities).

(3) **Quantitative approach** capable of indicating the *absolute* levels of infection. This would allow for intercomparison of levels *across* communities (which communities are showing the most acceleration or deceleration of Covid-19 — or of whatever infectious disease is targeted for monitoring). This more rigorous embodiment would provide the ultimate ability to reveal nationwide status and trends.

Developing the third approach, in particular, will depend on addressing the following primary questions. These questions become more challenging when the objective is to try and measure the incidence of active infection (on a per capita basis). The following are key:

- Required is a much better understanding of the intra- and inter-person variability in the magnitude of excretion (shedding) of detectable biomarkers from the virus in its infectious state (whether nucleic acids or proteins) — within-day, across days, and duration. The power of drawing conclusions from WBE monitoring will be a direct function of the range in these variabilities for individuals and the general population. The greater the variability, the harder it will be to determine if infections are from a few super-shedders or from a large portion of the population (e.g., see: [Chen et al., 2020a](#); [Pettersen, 2020](#); [Wu et al., 2020b](#)). It is possible that an antigen unique to SARS-CoV-2 might partition to excreta with more fidelity and better reproducibility. Furthermore, because of the duration of RNA excretion via the stool, it may not reflect active infections. This means that the collective signal of sewage RNA at any point in time might reflect unknown portions of active and past infections.
- If RNA is the targeted marker, there are currently too many unknowns surrounding the kinetics of viral load and excretion over the entire course of an infection ([Joynt and Wu, 2020](#)). To date, the published data on targeted markers for SARS-CoV-2 in feces (primarily RNA), or the viable virus itself, is insufficient for the modeling required for WBE. This is because nearly all of these data derive from clinical studies, which almost always use low numbers of case samples. A larger, randomized analytical study would be needed to shed more light on this important point. Currently, clinicians are motivated to monitor feces for four major clinical reasons (e.g., see: [Ianiro et al., 2020](#); [Ng et al., 2020](#); [Xiao et al., 2020](#)): (1) A critical concern is whether infectious virus occurs in fecal microbiota transplant samples, so mandatory screening could become important ([Ng et al., 2020](#)). (2) Concern exists as to whether the fecal-oral transmission route could prove significant. (3) Feces could become an alternative route for clinical diagnostic testing for Covid-19. (4) In many cases, feces continue to test RNA-positive long after the respiratory tract tests negative, and it is therefore important to know whether these cases still pose an infection threat.
- Whatever the targeted marker(s) might be, the excretion-route distribution needs to be known (e.g., fecal versus urine). The limited studies to date indicate that the fecal route is more important for SAR-CoV-2, at least for nucleic acids; but it is unknown for possible antigen targets. Likewise, the partitioning of a marker between feces and the liquid sewage needs to be established.
- The half-life (persistence) of the marker in wastewater must be known. It cannot be too long, otherwise it would be a trailing measure of infection, as its levels would be less prone to concentration change in sewage. Persistence is partly a function of temperature.
- The prior two points will dictate how representative-sampling must be performed — especially given that raw sewage is heterogenous.

The aqueous phase is a far more easily sampled medium and requires far less preparation for analysis.

- The sampling and analytical approaches will range from simple batch methodologies (where individual samples are collected) to time-integrated sampling and continuous monitoring (which would more closely represent “real-time” monitoring). The latter would pose far more challenges to develop but would be amenable to remote data collection. Indeed, sewer networks have already been undergoing automation, primarily for maintenance and remote control. However, much development has already been devoted to a wide range of sensors for parameters important to sewage treatment (e.g., see: [Setford et al., 2018](#)). This could provide an existing platform within which WBE sensors could eventually be integrated to fully automate monitoring and its remote reporting.
- For a quantitative approach, it is important to know the population size that contributes to an individual sewage treatment plant (to calculate the percentage of infected population). This can be an extremely onerous problem ([Daughton, 2012b, 2018](#)). Important to keep in mind is that an endogenous, excreted proxy marker for per capita population would remove the need to know the population size of a sewershed and could prove more accurate for estimating real-time population size ([Daughton, 2018](#)).

Addressing each of these points would be required for *calibrating* any WBE monitoring method so that data could be related to actual per capita infection rates. A number of different means have been proposed, the inverse regression of qPCR cycle thresholds with known infection rates being one example ([Bar Or et al., 2020](#)). Only if calibration could be achieved, would WBE then be able to reliably estimate the total number of infected people at any given time. It would then also be enabled to compare the infection rates *between* communities — facilitating the prioritization of resources for control and mitigation.

Finally, note that a major difference between WBE and mass diagnostic testing (such as via pooled samples) is that self-selection bias would not play a role in WBE, in contrast with diagnostic testing.

4. The risks posed by insufficient monitoring data

Perhaps never before in history have the economies and cultures of societies depended so much on the availability of analytical methods for the fast, reliable, inexpensive testing for a contagious disease. Without test data, governments cannot respond appropriately or efficiently. Nor can it be quickly learned whether suppression, containment, or mitigation countermeasures have been effective. There is no other way to intelligently mount effective responses in a timely manner. The only alternative tool is blunt-force, en masse quarantines or onerous lock-downs; note, however, that a few countries (e.g., Taiwan, Singapore, and South Korea) have successfully avoided lock-downs by using rigorous contact tracing ([Watson et al., 2020](#)). Never before has the lack of sufficient analytical testing methods caused so much havoc.

Even the perceived shortage of population-wide infection data can breed public distrust, anxiety, and even fear. A lack of data can lead some to conclude that data is being withheld or censored — further exacerbating distrust. In the absence of sufficient testing, the resulting void risks being filled by counter-productive personal beliefs, conspiracy theories, and politicization.

Isolation policies and physical distancing can lead to a sense of anger and personal grievement. One outcome is public unrest and defiance of suppression and mitigation measures, imposing additional stress on law enforcement and increasing the burden for more contact tracing and greatly endangering already over-stressed healthcare workers. Finally, democracies depend on un-suppressed, fully accessible voting. A

public that feels unsafe to vote can self-suppress; even voter registration can be suppressed. It is imperative that the public trust is ensured by establishing credibility and a reputation for safety. In addition, this is best accomplished through a well-conceived and transparent nationwide testing system.

The biggest challenge caused by insufficient testing surrounds the imperative to restart economies after periods of protracted isolation. Economies simply cannot recover until the public is convinced that the risk of transmission from Covid-19 has sufficiently diminished – or, alternatively, that it is clear exactly where the dangers remain. This cannot be readily or easily done with diagnostic testing alone (based on nucleic acid/antigen, with or without antibody) – although some emerging test technologies may hold promise (e.g., [NAS, 2020](#); [Zhang et al., 2020b](#)). Businesses, financial institutions, and the public must be convinced that hidden, asymptomatic contagious populations are confined or minimized. Just a mere 4 months into the Covid-19 crisis, this started to become obvious to governments and financial markets.

Simply because the intimate connections between public health and economic health are obvious, the temptation exists to focus on both at the same time. However, decisions to re-open economies prematurely can result in rebound of widespread infection ([Kissler et al., 2020](#)), resulting in yet further economic and public health damage. WBE could facilitate the properly timed and targeted shutdown and re-opening of specific geographic areas, especially if this must become an alternating episodic strategy for the duration of a pandemic. WBE would also avoid the problems in individual diagnostic or surveillance testing caused by missing those individuals who eschew testing or because they lack the means to seek or be tested.

5. National involvement and coordination of WBE R&D across nations

The profound and wide-ranging adverse impacts of Covid-19 rapidly unfolded worldwide in a matter of months. Even once the current rate of transmission had significantly declined, the possibility of repeated resurgence – especially coupled with common seasonal infectious diseases – cannot be underestimated. Moreover, pandemics caused by future novel infectious agents would add greatly to what could become a continual, looming threat to world stability.

Science typically advances in incremental, evolutionary steps, often catalyzed by competition between research groups. Revolutionary advancements also occur, but much less frequently. The fight against Covid-19 will require greatly accelerated development of an armamentarium of tools across a wide spectrum of disciplines in the sciences, medicine, and engineering. Advancements in WBE alone will require collaboration and coordination not just within individual disciplines, but also across disparate disciplines that traditionally are separate: analytical chemists, immunochemists, biochemists, environmental and civil engineers, wastewater treatment operators, computer modelers, statisticians, clinical scientists, pharmacologists, infectious disease specialists, public health experts, microbiologists (particularly virologists), epidemiologists, social scientists/psychologists, and communication/messaging experts (especially risk communication), among others.

One particularly important aspect of communication pertains to the perception of risk by the public. When WBE is applied to surveillance of infectious disease, clarity is essential in that WBE is not being used to monitor for viable, infectious virions (colloquially called “live” virus and which must instead be determined by traditional plaque-based assay), but rather to monitor for remnants of virus particles that serve as definitive indicators of active infections. This distinction is important for preventing public anxiety from the erroneous belief that “live” virus is rampant in sewage and could be released to surface waters.

Scores of local WBE pilot projects targeted at Covid-19 have been started or planned in cities around the world. However, this does not promote leveraging of worldwide knowledge and best practices, nor is it efficient at promoting uniform, standardized WBE for adoption at

national scales. The research and development needed to advance WBE for fighting Covid-19 would benefit greatly from national and international direction, coordination, and government funding ([Daughton, 2020a](#)); the World Health Organization could also play a major role. A unified worldwide plan would also help to minimize duplicative efforts and conserve resources. The ultimate objective would be to develop standardized, optimized, quality-assured WBE testing protocols that could be implemented worldwide – optimally as nationalized networks; few efforts to date have been directed at standardization and inter-laboratory studies (e.g., see: [WRF, 2020](#)). Standardized testing would be critical for promoting intercomparisons of all monitoring data – at local, state, regional, national, and cross-nation levels. All future advancements and best practices could be continually incorporated into harmonized methods. Furthermore, a geographically fragmented WBE data collection and reporting system would pose the same problems that already plague some clinical diagnostics networks at the national scale ([Patel, 2020](#)). To facilitate the development of globally harmonized methodologies, proprietary monitoring systems should be discouraged. An open-source model is essential to encourage wide adoption and minimize cost.

A Manhattan-style project might indeed be an apt metaphor for what is needed to fight Covid-19. Any type of such a big-science project (e.g., [Cahill et al., 2020](#); [Copeland, 2020](#)) needs to consider incorporating WBE in its full spectrum of potential strategies.

Another focus would be in determining how to best communicate WBE monitoring data to the public while minimizing panic or anxiety. This points to the need for science writers and other experts to publicly communicate WBE advancements and how WBE data should be interpreted. Finally, it would be important to locate those having intense interest in the potential of WBE and who could serve as its shepherds or champions to attract interest or involvement of politicians, military leaders, and other government officials concerned with public health, financial stability, and national security. Noteworthy is that over the last 15 years, WBE has been championed primarily by European countries and Australia for the purpose of monitoring illicit drug use; see discussion and references cited in [Sims and Kasprzyk-Hordern \(2020\)](#). Only a few national coalitions or efforts have been launched for Covid-19, three examples being Australia ([WaterRA, 2020](#)), Canada ([CWN, 2020](#)), and Spain ([Idrica, 2020](#)); the European Commission's Joint Research Centre and the Directorate-General for Environment is assessing the feasibility of an EU-wide WBE program ([European Commission, 2020](#)).

In the U.S., however, WBE has received little national reception. While some municipalities and sewage treatment plants in the U.S. have shown interest in piloting WBE for local Covid-19 tracking (e.g., see: [City of Tempe, 2020](#)), state and federal governments in the U.S. have expressed surprisingly little interest. Only as of this writing has any indication begun to emerge that U.S. federal agencies (i.e., the CDC and EPA) might be interested in WBE for Covid-19 ([Swan et al., 2020](#)).

Important to note is that the published science literature (as well as science news; see: [Arnaud, 2020](#); [Baggaley, 2020](#); [Mallapaty, 2020](#)) on WBE for monitoring infectious disease has begun an extremely rapid phase of growth – one that will undoubtedly escalate. It could prove increasingly time-consuming to track and assimilate this new base of emerging knowledge – as well as the plans for new research or demonstration projects. A centralized database of all known publications and preprints on WBE, as well as gray literature such as reports, dissertations, web pages, and news stories would prove extremely useful; note that the World Health Organization maintains a database of publications on all aspects of Covid-19 and that it currently comprises over 15,000 articles ([WHO, 2020b](#)). This is an astonishing number of published articles over a period of roughly only 4 months and marked by numerous major events surrounding Covid-19 ([Anonymous, 2020](#)); the primary focus of these articles is on the epidemiology, diagnostics, and clinical medicine of Covid-19 – not on WBE.

Another example of an attempt to compile a bibliographic database was done for the field of research concerning pharmaceuticals as environmental contaminants, including WBE (Daughton and Scuderi, 2017); this resource greatly facilitated the synthesis of existing knowledge for emerging pollutants, but such a project requires concerted, continual effort. Also note that a dozen of the references cited in this paper were preprints, many of which had not yet undergone peer review. However, because of the increasing numbers of preprints being posted, the major preprint servers have increased their internal screening and vetting processes (Kwon, 2020).

To maximize the usefulness of this new knowledge and to facilitate its uptake by news media (which, in turn, is key to cultivating interest and attention among the public and government officials), one particular coordinated action from the existing international community of WBE scientists would be very useful and could catalyze a formalized effort for international coordination. This action would at first simply involve the creation of a web-based database that would serve as a clearing house for all existing and planned R&D activities surrounding the application of WBE to Covid-19 (and possibly other infectious diseases). This clearing house would be populated by information solicited from, or provided by, WBE principal investigators worldwide. As existing efforts to enhance collaboration and support of WBE Covid-19 research grow (e.g., Bibby, 2020; Pérez-Escudero et al., 2020), they could be unified under a single umbrella.

Such a clearing house would also provide a current database of knowledge relevant to all aspects of WBE for monitoring infectious diseases (focusing on Covid-19 at the beginning). The purpose of this knowledge database would be to identify all knowns as well as research needs and gaps. This would inform the development of a comprehensive research strategy (guided by milestones) — one with flexibility as new, unanticipated knowledge emerges. As a very simple example, a list of questions and research needs with respect to Covid-19 has been compiled for guiding the needs of the U.S. Department of Homeland Security (DHS, 2020); but the priorities of DHS do not include most of those relevant to WBE.

Of course, global cooperation would probably never be comprehensive. It is aspirational. As already witnessed with this pandemic, some governments at local, state, or federal levels would inevitably not want to publicize WBE data — for fear of tarnishing their image, fear of causing public alarm, or for political reasons. Many governments would simply not have the needed resources. The major objective would be to get WBE deployed as widely as possible.

No one knows how long SARS-CoV-2 virus will be with us. Both old and novel viruses, however, inevitably find their way to the pandemic queue.

Declaration of competing interests

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. CGD is the sole author of this manuscript and declares no conflict of interest.

Acknowledgment

The work was unfunded. The work had no affiliation with any public or private entity. The author thanks the anonymous peer reviewers for their input.

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