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Future perspectives of wastewater-based epidemiology: Monitoring infectious disease spread and resistance to the community level

Natalie Sims, Barbara Kasprzyk-Hordern*

Department of Chemistry, University of Bath, Bath BA2 7AY, UK
Centre for Doctoral Training in Sustainable Chemical Technologies, University of Bath, Bath BA2 7AY, UK

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ABSTRACT

Infectious diseases are acknowledged as one of the most critical threats to global public health today. Climate change, unprecedented population growth with accelerated rates of antimicrobial resistance, have resulted in both the emergence of novel pathogenic organisms and the re-emergence of infections that were once controlled. The consequences have led to an increased vulnerability to infectious diseases globally. The ability to rapidly monitor the spread of diseases is key for prevention, intervention and control, however several limitations exist for current surveillance systems and the capacity to cope with the rapid population growth and environmental changes. Wastewater-Based Epidemiology (WBE) is a new epidemiology tool that has potential to act as a complementary approach for current infectious disease surveillance systems and an early warning system for disease outbreaks. WBE postulates that through the analysis of population pooled wastewater, infectious disease and resistance spread, the emergence of new disease outbreak to the community level can be monitored comprehensively and in real-time. This manuscript provides critical overview of current infectious disease surveillance status, as well as it introduces WBE and its recent advancements. It also provides recommendations for further development required for WBE application as an effective tool for infectious disease surveillance.

1. Introduction

Even with the advancement of infectious disease surveillance over the last century, communicable diseases still pose significant risks to public health. On the World Health Organisations (WHO) top 10 threats to global health in 2019, four on the list directly refer to infectious diseases: pandemic influenza, HIV, dengue and another for high-threat pathogens such as Ebola (World Health Organisation, 2019). Emerging infectious diseases caused by novel pathogenic organisms are of notable concern, it was highlighted by WHO that since the 1970s, over 1500 new pathogens were discovered and nearly 40 new infectious diseases have been identified (World Health Organisation, 2018a). Many of these have severely impacted communities, with several major outbreaks occurring within the last 20 years including severe acute respiratory syndrome (SARS) (2002–2003), Ebola (2014–2016), H1N1flu (swine flu) (2009–2010), Zika virus (2015–2016) and COVID-19 (2019–2020) (World Health Organisation, 2020a). Two others on this list are regarding the prevention and treatment of infectious disease, one being hesitation to vaccinate and the other the rise in antimicrobial resistance (AMR), both have been linked to the re-emergence of communicable diseases.

There are a number of drivers affecting the emergence and re-emergence of infectious diseases (Woolhouse and Gowtage-Sequeria, 2005). These range from climate change, poverty and unprecedented population increases with uncontrolled urbanisation. Another driver is globalisation linked with tourism and trade, resulting in a strong network of air links. With regards to international flights it has been highlighted that the incubation period of any human disease is still longer than the lengthiest aviation time for any international flight (Frenk and Gómez-Dantés, 2002). Outbreaks are therefore not confined to one geographic location but are less than 24 h away from being a threat somewhere else.

Another key factor for the re-emergence of infectious diseases has been linked with drug resistant pathogens. Whilst microbial evolution happens naturally, inappropriate usage of antimicrobials puts additional selective pressures and further facilitates rates of resistance (Allen et al., 2010; Andersson and Hughes, 2014). Whilst antibiotics tends to be focused on in discussions of AMR, rising cases of both fungal and viral resistances still pose significant threats (Fisher et al., 2018). For example, *Candida auris,* an emerging multidrug resistant yeast, is a cause of major hospital acquired infection with high associated mortality, having only first been identified in 2009 it has resistance to all

* Corresponding author.
E-mail address: b.kasprzyk-hordern@bath.ac.uk (B. Kasprzyk-Hordern).

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Table 1
Routes to assessing public health and infectious disease surveillance techniques with advantages and disadvantages.

Technique	Examples	Advantages	Disadvantages	References
Sentinel Surveillance	General practitioner's (GPs) reporting cases of influenza	Making use of an efficient system that is already in place Increase communication within communities Can help detecting larger health problems in a population	Rare and novel microbes occurrences are likely to be missed, e.g. new emerging virus Often focus on specific diseases	(Lee et al., 2010)
Clinical-based surveillance		Increased knowledge transfer between epidemiologists and microbiology laboratories Detailed information found on specific details of microbe e.g. virulence Online reporting available for specific diseases and up-to-date global databases publically available e.g. FluNet from WHO (https://www.who.int/influenza/gisrs_laboratory/flunet/en/)	Requires significant facilities, resources, trained staff and good communication links. Central reference laboratory is needed for standardisation and support If pathogens are rare, can lead to staff being complacent Selection bias on which samples are sent to the laboratory	(Choi, 2012)
Questionnaires or surveys	Recurrent or cross-sectional surveys	Can collect data for multiple diseases or exposures at one time Capability for local, national or international level Standardised methods utilised and high quality data often obtained Flexibility in questions asked Build up trends if survey is done repeatedly	Bias More information about public health Expensive – costs will vary on sample size, time period of survey Time delay to results If optional might not get a good response – might not be representative of whole populations Results can be difficult to interpret	(Thacker and Berkelman, 1988)
Search engine trends	Google Flu Trends (http://google.com/trends/)	Rapid obtainment of results Effective for large populations of web users Potential to track epidemics or diseases with high prevalence in a population	Difficult to determine if individuals searching are having symptoms or googling as concerned or to find out more Requires internet access, not as suitable for developing countries Differences in language backgrounds can lead to different words to describe symptoms being googled Diseases with low prevalence won't spike enough to notice	(Carneiro and Mylonakis, 2009)
Mortality and morbidity rates	Deaths recorded for diseases like Ebola or influenza	Inexpensive and well-established system of reporting Death certificates are legally required in most countries Can aid in monitoring the progression of an epidemic	If deaths from a particular cause are too low, mortality statistics potentially don't reflect accurate incidence of the disease Long delays in getting results Significant variation into how death certificates are filled Passive form of surveillance	(Choi, 2012)
Hospital admission data	ED-based surveillance for The Emerging Infectious Disease Surveillance Network	Can provide data on severity of injury, new emerging infectious disease and drug abuse Help identify if changes in healthcare are needed Potential early flagging of bioterrorism attack	Significant human and resource investment for setting up system and connecting with public health system Confidentiality challenges in sharing information to public health agencies Compliance of often busy emergency department staff to fill in data Need to standardise data collection	(Hirshon, 2000)
Prescription Rates		Generate trends of dug patterns in a community	Prescription data not always easily accessible Potential under-representation of what's being used - Over-the-counter drugs - Prescription medications can be bought without prescription - Hospital data is not captured Cannot know if patient has taken drug	(Cadarette and Wong, 2015)
Human bio-monitoring	Assess an environmental exposure of a toxin	Information received detailed and of high quality Can assess suspected exposure of an individual If collected repeatedly can build up exposure pattern over time.	Small focus group – might not be representative of a large population Selection of control group is challenging Lengthy ethical considerations, samples collected must be used for specific research project – further approval and consent needed for new analysis	(Bauer, 2008; Needham et al., 2007)

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Table 1 (*continued*)

Technique	Examples	Advantages	Disadvantages	References
Wastewater-based Epidemiology	Assess exposure to chemicals at the community level	Capable of spatial and temporal trends Data in near-real time (potential for real time with biosensors) Information given on whole population Ethical considerations, does not require approval depending on size of urban area	Selection of biomarkers can be challenging Biomarker stability in wastewater Uncertainties related to contributing population and wastewater flows Significant time-lag between data collection and analysis	(Been et al., 2017; Choi et al., 2019; Lopardo et al., 2018; Rousis et al., 2017)

clinically available antifungals (Lockhart et al., 2017).

The rising rate of resistance has resulted in AMR being hailed as one of the biggest public health risks threatening medicine in the 21st century (O'Neill, 2014). Increasing concerns of AMR have led to the establishment of the Global Antimicrobial Resistance Surveillance System (GLASS) in 2015 by WHO with the aims of sharing information on a global scale to strengthen data and aid decision making on national and international actions (World Health Organisation, 2015). Whilst the recent report (2017–2018) has revealed detailed results with participation from over 60 countries, several limitations in the study were discussed (World Health Organisation, 2018b). It was recognised that there was a lack of sampling strategy leading to selection bias, also patient samples are typically taken from those that have sought out medical care and hence might not be representative for a population. It was further highlighted the need to move away from laboratory data to include epidemiological and population data.

2. Current infection disease surveillance techniques and their limitations

Threats of (re)emerging infectious diseases along with rising rates of AMR reinforce that infectious disease surveillance is still an integral component of public health today. This has given rise to multiple techniques to monitor spatial and temporal trends of diseases.

2.1. Disease monitoring

There are several techniques with a range of advantages and disadvantages currently used for infectious disease surveillance (Table 1). Disease monitoring (which is often disease specific), can vary significantly with country and will depend upon the resources and sophistication of the public health services and facilities available (Thacker et al., 2006). The information collected can be provided to WHO, who have the authority to lead the global surveillance of infectious diseases. WHO have had an integral role in infectious disease surveillance, as well as leading international surveillance networks, e.g. influenza surveillance. They also provide international coordination of epidemic responses in diseases that pose significant public health risks. Examples of conventional routes to monitoring diseases are based upon existing resources, such as mortality and morbidity rates, prescription and hospital admission data. Whilst these are valuable source of information for surveillance purposes, they do suffer from bias, resource insensitivity and costs (Bauer, 2008).

Table 1. Routes to assessing public health and infectious disease surveillance techniques with advantages and disadvantages

Many of the current systems in place are forms of passive surveillance that have disadvantages. For example, in countries with less developed health services, morbidity might be higher than assumed due to people failing to report to a healthcare service due to lack of access. This combined with the fact that sometimes in epidemics the laboratory facilities can become easily overwhelmed – the consequence of such is that these cases are not reported. The 2009 swine flu epidemic caused by a H1N1 influenza virus spread rapidly to > 214 countries in the space of a few months. Whilst it was estimated that several million people were infected with over 18,400 confirmed laboratory deaths worldwide reported by August 2010 (World Health Organisation, 2010), it is believed that this is a gross underestimation. Reported studies in the literature have estimated through modelling techniques that there could have been as many as 10–15 times this amount, with up to 203,000 respiratory deaths (Dawood et al., 2012; Simonsen et al., 2013). Dawood *et al.* projected around 80% of these deaths occurring in Southeast Asia and Africa, the causes for underestimation have been attributed to poor reporting due to the overwhelming number of cases.

2.2. Infectious disease surveillance in growing urbanised nations

The problems underlying infectious disease surveillance will only be exacerbated. Current predictions have estimated a global population growth of 26% from 7.7 billion 2019 to 9.7 billion in 2050, with 68% of the global population expected to be urban (United Nations Department of Economic and Social Affairs, 2019). With the current unprecedented rises in population size, there will undoubtedly be further challenges (but also opportunities) in rapid health surveillance and response.

Therefore there is a need for a surveillance technique that (i) provides comprehensive and objective data, (ii) gives results in real-time, (iii) is flexible, (iv) able to monitor multiple diseases, even those that are rare, (v) is scalable and cost effective (vi) could be applied in low resource settings. Furthermore, the surveillance system needs to have comprehensive data collection systems regarding emergence of new diseases and re-emergence of old diseases, the threat of imported diseases or pathogens, and the emergence of multidrug or pan-drug resistant organisms. It has also been highlighted in the literature that monitoring clinics and laboratories for informing on public health is not sufficient, and there should also be an aspect of environmental monitoring of potential hazards (Nsubuga et al., 2006). Therefore, a surveillance technique that could also encompass environmental exposure would be invaluable in providing comprehensive exposure status and disease outcomes. A new surveillance technique utilising water fingerprinting is under the development to provide objective and comprehensive evaluation of both public and environmental health status in real-time.

3. Water fingerprinting via Wastewater-Based epidemiology - a new paradigm in public health assessment

Wastewater-Based Epidemiology (WBE) is a new approach utilised to give comprehensive health information on communities. The concept is primarily based upon the extraction, detection and then subsequent analysis and interpretation of chemical and/or biological compounds. These compounds, often referred to as biomarkers, could be harmful chemicals such as food toxicants and/or specific human excretion products (e.g. metabolites or endogenously formed chemicals as a result of exposure to and/or disease) that can be linked to the community as they are held within geographically defined water catchment areas (watersheds) to which whole populations contribute. Water sources that can be analysed are any that fall within the urban areas' catchment, and can include surface waters, domestic water sources and wastewaters. The results can then be used to give information on the community itself and its health, or environmental exposure. Wastewater is a popular and critical medium used in water fingerprinting. Often referred to as wastewater-based epidemiology (WBE), this technique can give an unbiased reflection on the community's health and lifestyle habits due to the rich source of biological and chemical information it contains (Kasprzyk-Hordern et al., 2014).

Wastewater-based epidemiology (WBE) – the basics. WBE postulates that endogenous and exogenous urinary human biomarkers identified and quantified in wastewater can give a reflection of the population's health in (near)-real time (Fig. 1). Wastewater (untreated) is usually collected from wastewater treatment plants (WWTP) as WWTPs serve communities located in well-defined geographical sewerage catchment areas. Usually, one WWTP serves a town or a city. Importantly, as a whole population contributes to wastewater collected by any WWTP, wastewater from this community can be considered as its pooled urine.

Fig. 1. Graphical representation of the wastewater-based epidemiology (WBE) concept

A critical consideration in WBE are wastewater flow rates which are key to account for due to the wide variations in influent flows (e.g. wet weather causing dilution). The consequence is of such that when reporting upon the presence of a compound, it is typical to report as the daily loads in wastewater (mg/day). Furthermore, to normalise and allow comparisons for cities in different geographic locations, with varying population size, the daily loads per capita may be reported instead (mg/day/1000 inhabitants). This process of back calculation of community-wide drug consumption or exposure to chemical factors can provide un-biased reflection of key aspects of public health. For example, the monitoring of pharmaceutical or illicit drugs in wastewater can detect subtle changes in trends in usage and consumption in a community. Furthermore, not only could spatial and temporal trends be established but such data could be monitored in real time, allowing deviations from usual trends to be spotted early. This offers several advantages over biomonitoring techniques which focus on small target groups due to expenses and logistical challenges such as ethical considerations, as WBE is done on a population-wide scale, the anonymity of individuals is maintained. Water fingerprinting can also offer more timely analysis than other traditional based public health approaches. This would allow public services to respond more rapidly and potential health interventions to be employed.

WBE and international collaboration. The field of WBE is a rapidly growing one and has experienced enormous successes since the idea was first conceived by Daughton in 2001 who hypothesised that the analysis of drug residues in wastewater could be linked back to population usage (Daughton, 2001). This was then first achieved in 2005 by Zuccato who successfully extracted and quantified cocaine in both wastewater and surface water and to investigate cocaine usage in the community (Zuccato et al., 2005).

A large number of international long-term monitoring initiative have since been established worldwide with the most active networks in Europe (European Monitoring Centre for Drugs and Drug Addiction, 2016; Thomas et al., 2012), Australia (Choi et al., 2019; Lai et al., 2018, 2016; O'Brien et al., 2019; Tscharke et al., 2016) and in the USA (Halden et al., 2019). The successes of WBE that have been demonstrated on global scales have given rise to discussions on future outlooks for the technique (Choi et al., 2018; Daughton, 2018; Kasprzyk-Hordern et al., 2014; Thomas and Reid, 2011). Initially, work was entirely focused upon illicit drug usage, including heroin, cocaine and methamphetamines (Boleda et al., 2007; Castiglioni et al., 2006; Kasprzyk-Hordern et al., 2008; Zuccato et al., 2008) but have since expanded to include a diverse range of other endogenous biomarkers, varying from ones linked to lifestyle choices such as alcohol consumption (Boogaerts et al., 2016; Reid et al., 2011; Rodríguez-Álvarez et al., 2014a), tobacco (Castiglioni et al., 2015; Lai et al., 2017; Rodríguez-Álvarez et al., 2014b; Tscharke et al., 2016) and psychoactive substances (Kinyua et al., 2015; Mardal and Meyer, 2014; Reid et al., 2014). Others have investigated general health through oxidative stress markers (Ryu et al., 2016, 2015; Sims et al., 2019).

Additionally, the analysis of metabolic urinary biomarkers of exposure in wastewater can reveal critical information upon community-wide exposure to external stressors accounted in everyday life. Examples of which can be exposure to chemical compounds such as endocrine disrupters, compounds that are known to effect hormone regulation, but that are typically not regulated (Testai et al., 2013). Chemicals found in personal care products and consumer products, including UV filters in sunscreen, plasticizers, flame retardants and pesticides are suspected or known endocrine disruptors. Frameworks investigating community exposure to such compounds have been developed through analysis of exposure metabolites within wastewater, results of which have already provided comprehensive international population-wide exposure data for pesticides (Rousis et al., 2017), flame retardants (Been et al., 2018, 2017), carcinogens linked to tobacco (Lai et al., 2017), UV filters (Lopardo et al., 2018), mycotoxins (Gracia-Lor et al., 2020) and BPA (Lopardo et al., 2019).

3.1. Challenges of wastewater-based epidemiology

Complexity of wastewater matrix. Whilst conceptually WBE is

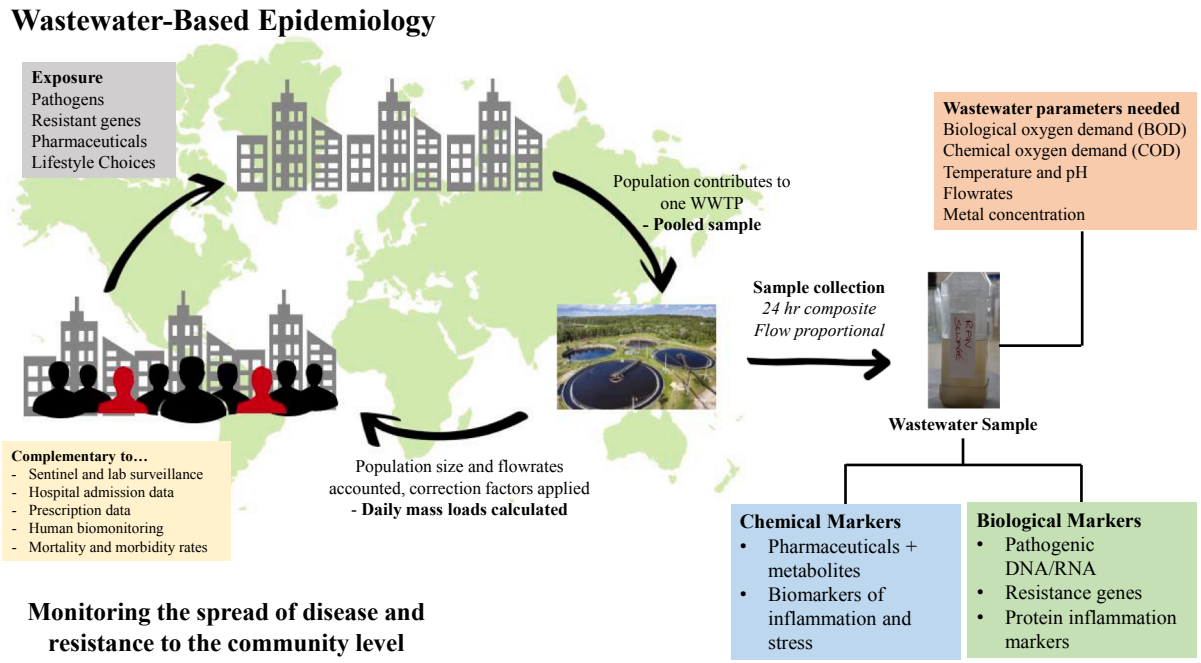

Fig. 1. Graphical representation of the wastewater-based epidemiology (WBE) concept.

very simple and clearly offers attractive advantages for the monitoring of public health, there are some challenges to be considered. For example, not only are the levels of biomarkers far more dilute in wastewater, especially in comparison to urine, but the wastewater matrix itself provides a complex environment to work in (Daughton, 2012). As previously mentioned, wastewater contains a diverse abundance of chemical and biological targets which can give incredibly detailed information about the population that contributes. However, a drawback to having such a large amount of information is in the successful extraction from the matrix itself and the subsequent analysis of specific targets can be difficult. Extraction methods such as solid phase extraction and immunoassay techniques along with sophisticated analytical tools such as advanced mass spectrometry have allowed for the analysis of a wide number of compounds (Petrie et al., 2014). Recent developments in sensing approaches could enable measurements on site, which would allow the system to provide information on public health in real time (Yang et al., 2017, 2016, 2015).

Estimation of population size. Another challenge associated with WBE is the problem posed by dynamic populations (e.g. population fluctuations due to tourism and commuters) (Ort et al., 2014). Typically the standard approach is for levels of certain endogenous biomarkers in humans, such as cortisol or cotinine, to be calculated as daily loads which have been normalised to the population. This enables inter-city comparison (Chen et al., 2014). However, there are difficulties in estimating the population size of individual WWTP catchments. This can result in unaccounted for, unique population fluctuations that, whilst having negligible impact on the levels of biomarkers in large populations (> 100,000 people), they might contribute to higher uncertainties in smaller populations.

There are several techniques that can be employed to reduce to the source of uncertainties associated with population size. Investigating certain hydrochemical parameters which have well-established methods of analysis, such as chemical oxygen demand (COD), biological oxygen demand (BOD) or ammonium (NH_4^+) can aid in estimating populations contributing to a WWTP catchment at a particular time period (Been et al., 2014; van Nuijs et al., 2011). These however can be influenced by the composition of wastewater. The other uncertainties associated with the technique briefly mentioned above with regards to sample collection and analytical variability amongst a couple of others, have all been extensively discussed in a number of reviews (Castiglioni et al., 2013; Ort et al., 2014, 2010). However, SCORE and the EMDCCA have demonstrated that with recognition of the limitations of the technique, that the development and adoption of a reliable, standardised method will give reliability and credibility to the studies and allow spatial and temporal comparisons to be made.

Uncertainties within population size will also pose problems for infectious disease surveillance within wastewater, as the presence of tourists or commuters within a catchment area could make it challenging to monitor the actual emergence of an infection within that community For example, it would be impossible to distinguish whether the presence of a pathogen in wastewater had stemmed from a visitor(s) passing though or from within the community itself. Arguably however, the presence of a pathogen in wastewater, whether from a resident in the catchment area or not, still provides critical information as members within the population may have been unknowingly exposed to the infected individual. This could indicate towards potential disease emergence within the community, allowing valuable time for appropriate preparation and response to be put into place.

3.2. Desirable characteristics in biomarkers

Endogenous and exogenous biomarkers in wastewater, when chosen carefully, can give key information with regards to health of a population. Along with some of the limitations of WBE touched upon above, there are also certain criteria that must be fulfilled for a biomarker to be considered in WBE techniques. For example, the biomarker in question must mostly be excreted via urine and concentrations of the biomarker must be in ng L^{-1} for downstream detection of the biomarker in wastewater (Chen et al., 2014). Another vital characteristic is that the biomarker needs to be stable, not only in the sewage system but also during the process of sampling and storage (McCall et al., 2016). Biomarkers also need to be unique to human metabolism and ideally the metabolism process involving the biomarker would be well understood. This ensures that the biomarker in question has only originated from human sources, as opposed to exogenous ones (potential contamination of animals in the sewage system or from microbes present in wastewater) (Daughton, 2012). With regards to the sewage system, wastewater is home to an extensive range of complex microbial communities

Table 2
Examples of potential biomarkers that could be used for monitoring infectious disease spread at the community level through wastewater

Biomarker Groups	Biomarker Examples	Treatment/indicator of	Reported Concentrations	Reference
Biomarkers of intervention	**Antibiotics**			
e.g. Drugs and metabolites	Sulfamethoxazole	Urinary tract infections, bronchitis	< 3–3100 ng/L (INF)	(Guerra et al., 2014; Hijosa-Valsero et al., 2011; Kasprzyk-Hordern et al., 2009)
	n-Acetyl sulfamethoxazole		360 ± 110 ng/L (INF)	
	Azithromycin	Pneumonia. middle ear infections, strep throat and intestinal infectios	269–22,730 ng/L (INF)	(Senta et al., 2019)
	n-*Demethyl azithromycin*		< 30–74 ng/L (INF)	
	Clarithromycin	Pneumonia, skin infections, H. pylori infection, and Lyme disease.	111–10,491 ng/L (INF)	(Senta et al., 2019)
	n- *Demethyl clarithromycin*		13–1559 ng/L (INF)	
	Ciprofloxacin	Respiratory tract infections, skin infections, gastroenteritis	17-2500 ng/L (INF)	(Guerra et al., 2014)
	Erythromycin	Respiratory tract infections	14–10,025 ng/L (INF)	(Guerra et al., 2014; Kasprzyk-Hordern et al., 2009)
	Trimethoprim	Urinary tract infections	464–6796 ng/L (INF)	(Kasprzyk-Hordern et al., 2009; Roberts and Thomas, 2006)
	Antivirals			
	Oseltamivir phosphate	Flu virus (influenza)	5–529 ng/L (INF)	(Leknes et al., 2012; Takanami et al., 2012)
	Oseltamivir carboxylate		28–1213 ng/L (INF)	
	Acyclovir	Herpes simplex virus infections, chicken pox, shingles	1780 ng/L (INF)	(Funke et al., 2016; Prasse et al., 2010)
	Carboxy-acyclovir		490–3420 ng/L (INF)	
	Emtricitabine	HIV	100–980 ng/L (INF)	(Funke et al., 2016)
	Carboxy-emtricitabine		24–250 ng/L (INF)	
	Lamivudine,	HIV/AIDs, hepatitis B	52–720 ng/L (INF)	(Funke et al., 2016; Prasse et al., 2010)
	Carboxy lamivudine		25–84 ng/L (INF)	
	Abacavir	HIV/AIDs	21–140 ng/L (INF)	(Funke et al., 2016)
	Carboxy-abacavir		41–560 ng/L (INF)	
	Zanamivir	Flu virus (influenza)	16.3–27.8 ng/L (INF)	(Takanami et al., 2012)
	Zidovudine	HIV/AIDs	310–380 ng/L (INF)	(Prasse et al., 2010)
	Nevirapine	HIV/AIDs	4.8–21.8 ng/L (INF)	(Prasse et al., 2010)
	Antifungals			
	Ketaconcazole	Skin infections	16 ng/L(INF)	(Huang et al., 2010)
	Miconazole	Skin infections	5.2–1583 ng/L (INF)	(Guerra et al., 2014; Huang et al., 2010; Kasprzyk-Hordern et al., 2009)
	Clotrimazole	Skin and vaginal infections	23-33 ng/L (INF)	(Huang et al., 2010; Roberts and Thomas, 2006)
	Painkillers			
	Acetaminophen	Painkiller	5529–500,000 ng/L(INF)	(Guerra et al., 2014; Roberts and Thomas, 2006)
	Ibuprofen	Painkiller	968–45,000 ng/L(INF)	(Guerra et al., 2014; Kasprzyk-Hordern et al., 2009; Roberts and Thomas, 2006)
Biochemical markers linked with physiological response	C-reactive protein (CRP)	Inflammation	0.54–2.76 μg/mL (Urine)	(Stuveling et al., 2003)
e.g. Biomarkers of inflammation	Interlukin-6 (IL-6)	Inflammation in urinary tract infections	1.6–5.28 pg/mL(Urine)	(Renata et al., 2013; Roilides et al., 1999)
	Interlukin-8 (IL-8)	Inflammation in urinary tract infections	7–12 pg/mL (Urine)	(Taha, 2003)
	Lipoarabinomannan (LAM)	Potential indicator of tuberculosis in HIV infected patients	15 pg/mL to several hundred ng/mL(Urine)	(Boehme et al., 2005; Hamasur et al., 2015; Savolainen et al., 2013)
	IP-10	Potential indicator of tuberculosis and pneumonia	5–110 pg/mL (Urine)	(Cannas et al., 2010; Kim et al., 2018)

(*continued on next page*)

Table 2 (*continued*)

Biomarker Groups	Biomarker Examples	Treatment/indicator of	Reported Concentrations	Reference
Pathogenic organisms	**Bacterial DNA**			
e.g. Pathogenic genetic material/ DNA/ RNA	*Klebsiella pneumoniae*	Pneumonia, UTI, bacteremia and endophthalmitis	6.31–6.56 log gene copies/100mL (INF)	(Shannon et al., 2007)
	Pseudomonas aeruginosa	Pneumonia, UTI, gastrointestinal infections	4.31–4.38 log gene copies/100 mL (INF)	(Shannon et al., 2007)
	Enterococcus faecalis	UTIs, bacteremia, septicemia	4.66–4.85 log gene copies/100 mL (INF)	(Shannon et al., 2007)
	Viral DNA/RNA			
	Norovirus (GI)	Gastroenteritis	< 10–3500 viral genomes/L (INF)	(Hellmér et al., 2014)
	Norovirus (GII)	Gastroenteritis	12.4×10^3–320×10^3 viral genomes/L (INF)	(Hellmér et al., 2014)
	Influenza A	Respiratory infection	2.6×105 genome copies/L (INF)	(Heijnen and Medema, 2011)
	Dengue	Severe flu-like illness	$4\text{-}5 \times 10^{-1}$ PFU/mL(Urine)	(Poloni et al., 2010)
	Zika	Mild infection, microcephaly	0.7–220.106 copies/mL (Urine)	(Gourinat et al., 2015)
	Hepatitis A	Liver infection	< 10-1500 viral genomes/L (INF)	(Hellmér et al., 2014)
	Severe acute respiratory syndrome (SARS CoV)	Respiratory infection	$< 1x10^1$-$10^{6.5}$ (Faeces)	(Poon et al., 2004)
	Fungal DNA			
	Candida species	Candidiasis	Detected * (INF)	(Assress et al., 2019)
	Aspergillus (Aspergillus fumigatus, Aspergillus niger and Aspergillus flavus)	Chronic pulmonary aspergillosis, pulmonary and nasal allergies, asthma, pneumonitis		
	Parasites			
	Giardia lambli	Small intestine infections	2,653– 13,408 cysts/litre (INF)	(Guy et al., 2003)
	Cryptosporidium	Gastrointestinal illness	1–120 oocysts/litre (INF)	(Wallis et al., 1996)
Biological response	*mcr-1*	Colistin resistance	8.11 × 101 cell equivalents/100 ng DNA (INF)	(Hembach et al., 2017)
e.g. Antibiotic resistant genes	*mecA*	Methicillin resistance	$1x10^1$- ~$5x10^4$ genes/100 mL(INF)	(Börjesson et al., 2009)
	ermB	Erythromycin resistance	$10^{5.2}$–10^7 copies/mL(INF)	(Wang et al., 2015)
	sul1	Sulphonamide resistance	$10^{5.46}$–$10^{7.54}$ copies/mL(INF)	(Munir et al., 2011; Wang et al., 2015)
	$bla_{OXA\text{-}1}$	Beta-lactam resistance	$10^{5.4}$–$10^{7.3}$ copies/mL (INF)	(Wang et al., 2015)
	tetW	Tetracycline resistance	$10^{4.2}$–$10^{7.4}$ copies/mL (INF)	(Munir et al., 2011; Wang et al., 2015)

INF: Influent wastewater (U): Urine. PFU: Plaque forming units (measure of number of infectious particles).UTI: Urinary tract infection *Via sequencing

that are challenging to characterise and will vary geographically. As of such, there is a high risk of microbial degradation or transformation of chemical compounds. In fact, biological treatment in wastewater treatment plants, such as trickle bed filters, are home to these diverse microbial communities which play a key role for the breakdown of many organic compounds (Kraigher et al., 2008).

4. Water fingerprinting for community-wide infectious disease diagnostics

WBE has already demonstrated successes in monitoring drug consumption, lifestyle choices and population-wide exposure. Several studies have discussed the future of WBE and the expansion to include biomarkers linked to other aspects of public health, including diet, stress, and biological based monitoring linked with illness (Choi et al., 2018; Daughton, 2018; Gracia-Lor et al., 2017). Due to the wide array of endogenous chemical and biological urinary biomarkers linked with disease, there is clearly huge potential for WBE to be utilised to monitor infectious diseases and the spread of epidemics at the community level (Table 2).

Table 2. Proposed key biomarkers for use in WBE to monitor spread of infectious diseases to the community level.

WBE could be utilised as a complementary surveillance technique which can give rapid, reliable information on a population that can inform what diseases are present in a community and could aid in monitoring disease outbreaks. It is of paramount importance to choose a wide-ranging panel of markers providing information on (i) pathogenic organisms (bacteria and viruses), (ii) biochemical markers linked with physiological response (endogenous markers e.g. biomarkers of inflammation including small molecules and proteins), (iii) markers of intervention (pharmaceuticals and their metabolites) biological response, (iv) markers of antimicrobial resistance.

4.1. Markers of pathogenic organisms

An example of a key biological marker are pathogenic DNA/RNA residues from bacteria, viruses and fungi. The detection in influent wastewater would suggest human sources and hence indicate what diseases are circulating within a population. Whilst risk factors for emerging infectious diseases have highlighted resistant bacteria as a concern, viruses pose a significant threat due to their high mutation rates and ability to adapt to new host, e.g. humans. This is particularly in the case of RNA viruses, where higher nucleotide substitution rates can result in this rapid adaption and spreading in new host populations (Woolhouse and Gowtage-Sequeria, 2005). The potential of wastewater to be used for viral surveillance has been well discussed in the literature (Barras, 2018; O'Brien and Xagoraraki, 2019; Wigginton et al., 2015). Wastewater surveillance has already demonstrated promising results with the potential for retrospective prediction of disease outbreaks of hepatitis A and norovirus (Hellmér et al., 2014). Influenza in wastewater was also investigated during the H1N1 (swine) flu virus outbreak, whilst influenza A viruses were detected in sewage, the pandemic H1N1 virus was not detected (Heijnen and Medema, 2011). Furthermore, environmental surveillance of polio in wastewater has been utilised since the 1980 s, years before when the term "wastewater-based epidemiology" was coined, with Finland (Hovi et al., 2012) Israel (Roberts, 2013) and Senegal (Ndiaye et al., 2014) all successfully analysing sewage samples in order to assess polio circulating within populations. WHO have also released guidelines for employing environmental sampling to monitor polio in wastewater samples (World Health Organisation, 2003).

The complexity of a wastewater matrix is not only challenging for the extraction and quantification of chemical compounds, similar problems are apparent for biological biomarkers. Composition of wastewater contains a diverse range of PCR inhibitors including fats, proteins and humic and fulvic acids, which can cause problems later during downstream processing during PCR. The availability of different commercial extraction kits for DNA/RNA has demonstrated sometimes variable efficiencies and consistencies when extracting from PCR inhibitor rich samples, including wastewater and sediments (Mumy and Findlay, 2004; Walden et al., 2017). This results in challenges when making meaningful comparisons across different studies and in establishing spatial and temporal trends. However, advancements of molecular biology techniques offer new routes for the analysis of genetic material, including digital PCR (dPCR) and next generation sequencing techniques. In dPCR, the absolute quantification of target genes is calculated using Poisson distribution statistics via the partitioning of DNA/RNA samples into tens and thousands of reaction wells. Due to this partitioning effect, PCR inhibitory substances have demonstrated to have less of an effect in environmental samples, including wastewater, when analysed via dPCR (Rački et al., 2014). Critical evaluation of dPCR and its suitability for certain sample types have been discussed by Salipante et al (Salipante and Jerome, 2020).

Next generation sequencing is another promising technology, providing a wealth of information on the complex microbial communities in samples, including identification of the diverse range of pathogens and resistance genes present. In particular, analysis of the viruses and resistance genes present via metagenomics has been highlighted as providing potentially key information on novel pathogens as well as re-emerging infectious diseases and AMR (Aarestrup and Woolhouse, 2020; Fernandez-Cassi et al., 2018). Whilst standardisation of protocols of metagenomics remain a challenge, the continued advancements in the technology combined with decreasing costs sequencing have the potential to revolutionise both pathogen and resistance surveillance in wastewater.

4.2. Biochemical markers linked with physiological response

Protein based inflammation biomarkers represent a vital group of endogenous markers. Urine proteomics has attracted much interest in the last decade as has been evidenced to contain an abundant source of proteins. Urine for diagnosis purposes is desirable not only due to the non-invasive nature of testing but because of the previously untapped source of potential disease and health biomarkers (Zhao et al., 2017). Some which could be sensitive to changes in the body and could be early indicators of disease. Whilst only a handful of proteins are currently utilised in clinics, it has been previously highlighted that this is not a limitation for WBE, as purposes here are not for diagnostic analysis (Daughton, 2018). Urinary inflammation biomarkers that are indicative of inflammation include C-reactive proteins (CRP) and interleukins including IL-6 and IL-8, have been highlighted as promising candidates for use in WBE (Rice and Kasprzyk-Hordern, 2019). Urinary CRP levels are routinely utilised in clinics and in human biomonitoring studies, e.g. to investigate renal function abnormalities within a population (Stuveling et al., 2003). Other proteins that have previously been suggested for WBE include vitamin D binding proteins, which are prognostic biomarkers for kidney disease due to their significantly elevated levels occurring in the urine of infected individuals (Daughton, 2018).

Increased interest into urine proteomics for non-invasive clinical tests is a growing area and with it will bring greater understanding of the proteins present in urine. Whilst it is widely considered that proteomics in WBE would offer invaluable new insight into public health of communities, the analysis of proteins in wastewater however is still underexplored (Rice and Kasprzyk-Hordern, 2019). The extraction and analysis of these larger biomolecules from wastewater poses new analytical challenges due to the complexity of the matrix, and questions regarding stability of proteins in the sewage systems are yet to be investigated.

4.3. Markers of pharmacological intervention

Biomarkers of intervention encompass pharmaceuticals used to treat infectious diseases or ones used to lessen the symptoms. As previously mentioned WBE has been successful at monitoring drug usage, and as

many infectious diseases are seasonal, there are potentially interesting opportunities for trends to be established in wastewater. Regarding antibiotics, a handful of studies have demonstrated seasonal patterns for several antibiotics, including clarithromycin, erythromycin and ciprofloxacin with higher loads typically observed over winter (Coutu et al., 2013; Golovko et al., 2014). This is in line with the use of these antibiotics for respiratory infections where cases tend to peak in winter-early spring. In areas where prescription data is not widely available or antimicrobial medications can be bought over the counter with ease, WBE could provide a route for monitoring antimicrobial usage within a community which otherwise might go unobserved.

With rising rates of AMR, the importance of understanding consumption habits in a community is critical, one of the major advantages of WBE is the potential to distinguish differences between prescription and consumption of a pharmaceutical. Investigating ratios of parent compounds to respective metabolites or ratios between compound enantiomers in wastewater can inform on whether levels have originated from human excretion or from direct disposal of a pharmaceutical into the sewage system (Petrie et al., 2016). Furthermore the availability of pharmacokinetics data and excretion rates can allow back calculation to the estimated amounts of a pharmaceutical that a population has ingested (Zuccato et al., 2008). This ability to distinguish between prescribed, disposed and consumed is important as just because a pharmaceutical is prescribed does not necessarily mean it is used. Delayed prescribing is a strategy by which a general practitioner (GP) will make a prescription available but will ask the patient to delay from using in order to see if symptoms improve first. The initiative has been evidenced to successfully reduce antibiotic usage in a handful of countries, including New Zealand, Norway and England (Spurling et al., 2013). The use of WBE could therefore give valuable insight into the amounts of antimicrobials a population has actually consumed. However, whilst the analysis of parent compounds to metabolites provides valuable community usage data, the analysis of antibiotic metabolites tends to be overlooked in wastewater analysis, with parent antibiotics typically focused on.

With regards to resistance, further research is needed to understand how antibiotic usage in communities is impacting the bacterial communities in WWTPs. It is well recognised that WWTPs are hotspots for resistance but the long term effects of exposing microbes to sub-inhibitory concentrations of antibiotics in wastewater streams is not well understood (Andersson and Hughes, 2014; Michael et al., 2013).

When compared to antibiotics, the prescription pattern of antivirals can differ as they are often less commonly prescribed on a day-to-day basis. For example, antivirals like Tamiflu® and Relenza®, are stockpiled globally and are then deployed during pandemic periods which can result in high proportion of a community taking the drug in a short time window which is reflected in wastewater (Singer et al., 2007). During the H1N1 influenza virus pandemic in 2009, Tamiflu® (oseltamivir phosphate) was heavily prescribed globally in response. It has been reported that oseltamivir carboxylate, a biologically active and persistent metabolite of oseltamivir phosphate, was observed in surface waters during peaks of the outbreak (Leknes et al., 2012). This was due to increased loads of the metabolite in wastewater, which is widely known to not be readily removed by conventional WWTPs.

The monitoring of drugs like antivirals and their metabolites not only informs upon drug compliance and the progression of an outbreak at the community level, but like with antibiotics, could provide critical information with regards to resistance. The presence of these drugs or their metabolised forms in low levels in the environment could cause irreversible effects to the viral genome resulting in resistant effects. For example, it has been highlighted the guts of wildfowl could be potential oseltamivir carboxylate-resistance hotspots due to exposure to the metabolite in surface waters (Singer et al., 2007). The rapid spreading of the H1N1 virus and the ease of which viruses can become resistant to antivirals stress the importance of population-wide surveillance tools and again the importance of combining chemical analysis with biological. Furthermore, whilst a number of antiviral drugs have been detected in water bodies, there is still a knowledge gap of understanding the environmental impacts their presence has in wastewater streams, especially as they tend to pass through WWTP unchanged (Jain et al., 2013).

4.4. Markers of antimicrobial resistance

Markers of antimicrobial resistance are another group of key biological biomarkers. The analysis of antimicrobial resistance genes (ARGs) in influent wastewater could provide a broader perspective of the resistance genes present within a population. This together with viral and bacterial monitoring arguably could give a more representative reflection of health of a community, as currently much of the understanding of both diseases and resistance circulating within in a community are based upon clinical samples. The results from clinics are often from a very small proportion of the population who are ill and hence not representative of the population as a whole, as many people can be carriers of a disease or a resistance gene and not experience symptoms (asymptomatic in case of diseases). As previously mentioned, it was highlighted by WHO's GLASS programme that a limitation is that current samples are focused on a clinical level and more epidemiological information on a population scale are needed for AMR surveillance purposes (World Health Organisation, 2018b).

WBE could aid in providing this population-wide information, to date a diverse range of ARGs have been studied and reported on in wastewater, typically through qPCR techniques (Mao et al., 2015; Rodriguez-Mozaz et al., 2015; Sun et al., 2016; Zhang et al., 2009). Only a handful of studies to date have investigated relationships between the levels of antibiotics and abundance of ARGs in wastewater streams, Correlations observed between antibiotic and respective resistance gene levels have been antibiotic dependant with some correlations observed (Gao et al., 2012; Novo et al., 2013; Rodriguez-Mozaz et al., 2015; Xu et al., 2015). However, it is generally recognised that the relationship between antibiotic concentrations and resistance in wastewater is complex with further studies needed. Furthermore, focus tends to be upon more common antibiotics resistances, such as sulphonamides, tetracyclines and quinolones, hence there is still a knowledge gap regarding other antimicrobial classes of AMR genes, including those associated with antifungal resistance. The effects of seasonality upon ARGs in wastewater is another underexplored area, though Caucci et al. reported strong seasonal abundances of ARGs within wastewater, with higher levels observed in Autumn and Winter which coincided with increased antibiotic prescribing in those months (Caucci et al., 2016).

Further work is needed to consolidate the impacts of antimicrobial prescribing at the community level on the abundance of ARGs in wastewater, particularly if this is to be utilised for epidemiology purposes. Establishing this link is recognised as challenging as several factors will potentially influence the abundance of ARGs in sewers other than the selective pressures from antimicrobials being prescribed. For example the environmental conditions in sewers has been shown to potentially impact ARG abundance, including temperature, metal pollutants and changes in composition of microbial communities (Jiao et al., 2018; Novo et al., 2013; Sun et al., 2016).

5. Ethical considerations

As with many other scientific innovations, WBE is not immune to misuse and misrepresentation. As WBE does not collect data on individuals, the ethical risks are low. However, it will be necessary to manage privacy issues and the potential for stigmatisation of certain societal groups. The ethical aspects of WBE for pharmaceuticals have been discussed elsewhere (http://score-cost.eu/ethical-guidelines-for-wbe/). It is generally accepted that populations over $>$ 10,000 is enough to give anonymity and will pose no risk to smaller groups of people. This is also relevant in the case of publications to reduce any risk of media misinterpreting the publication's finding.

Expanding WBE to include infectious diseases will pose new challenges to the ethical considerations, particularly with regards to disease outbreaks. With regards to pathogen monitoring in wastewater, population size will be important. It has been highlighted by WHO for the case of monitoring polio in wastewater that large populations may decrease sample sensitivity and therefore sampling from subgroups may be required (World Health Organisation, 2003). As infectious diseases, such as polio, spread rapidly in urban areas, the sampling of subgroups might also provide faster interventions by public health authorities. However, sampling from smaller subgroups in cities could lead to stigmatism of vulnerable groups.

Furthermore, outbreaks and the subsequent handling of them will differ between developing and developed countries due to the availability of resources and the quality of health and regulatory infrastructures in place. However, any outbreak, regardless of geographic location are fragile situations. Thus, care must be taken in the reporting of diseases being investigated within a community and social understanding of the situations will be crucial. For example, fear-trigged behaviours have been attributed as one of the major contributing factors to the spread of Ebola in Western Africa (Shultz et al., 2016). Stigmatism surrounding individuals infected with Ebola combined with a sense of distrust in health services and treatment centres resulted in efforts to hide cases. This exacerbated the Ebola spread, as there was a decreased chance of survival of those infected with home treatment and increased chances of infecting family members or carers which in turn could infect other members of the wider community.

Similar ethical issues have also been observed with outbreaks such as SARS, influenza and tuberculosis, which has resulted in WHO publishing the first comprehensive international ethics guidelines on public health surveillance in 2017 (World Health Organisation, 2017). These can be appropriately adapted to different social, economic and epidemiological circumstances. As WBE continues to expand in the direction of disease monitoring, ethics should be considered and developed alongside. Ethics guidelines will need to be adaptable, and consider factors such geographic location, population and the biomarkers to be monitored to enable further development of this field.

6. Conclusions

It is widely acknowledged that effective surveillance systems are key for the rapid intervention and control of infectious disease outbreaks. There is also a requirement for population-wide surveillance information to compliment current clinical data. WBE has demonstrated significant promise in providing information on community-wide exposure and health status comprehensively and in near real-time. The importance of effective surveillance has been highlighted recently with the case of the novel coronavirus (COVID-19). On the 31st December 2019, a number of cases of pneumonia of an unknown cause were detected in Wuhan City in China. Just a week later on the 7th January Chinese officials had reported a novel strain of the coronavirus (World Health Organisation, 2020b). Even with early intervention measures of quarantining cities in China and travel bans, by the 3rd March 2020 the number of confirmed cases were 90,892 across 73 countries with severe outbreaks occurring in South Korea, Iran and Italy (World Health Organisation, 2020c). Along with the current routes of global surveillance for the virus, WBE, if implemented, could track spread of the virus and, if linked with effective response system, could help with management. However, in order to successfully apply WBE in infectious disease surveillance, rapid advancements are required to tackle some of key challenges. These include:

- complexity of wastewater matrix and the need for new biomarker extraction techniques,
- difficulties in accurate estimation of population size to account for temporal population size fluctuations,
- non-existent biomarker discovery pipeline for both chemical and biological markers
- lack of analytical tools for cost-effective, sensitive, selective and multi-residue analysis of wide-ranging biomarker groups spanning from genes through to proteins and whole microorganisms.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105689.

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