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Review article

Opportunities and limits of wastewater-based epidemiology for tracking global health and attainment of UN sustainable development goals

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ABSTRACT

Wastewater-based epidemiology (WBE) emerged as a powerful, actionable health management tool during the COVID-19 pandemic. Hypothesizing future uses, we explored its potential for real-time, tracking of progress in attaining United Nations Sustainable Development Goals (SDGs) globally as a non-expensive method using existing infrastructure. We inventoried (*i*) literature-documented sewerage infrastructure, (*ii*) demographics of populations served, and (*iii*) WBE markers informative of 9 SDGs. Among the 17 different sustainable development goals listed by the UN 2030 agenda, more than half of these may be monitored by using WBE monitoring at centralized treatment infrastructure as tabulated in this study. Driven mainly by COVID-19, WBE currently is practiced in at least 55 countries, reaching about 300 million people. Expansion of WBE to 109,000 + treatment plants inventoried in 129 countries would increase global coverage 9-fold to 34.7% or 2.7 billion, leaving out 5 billion people not served by centralized sewerage systems. Associations between population demographics and present-day infrastructure are explored, and geospatial regions particularly vulnerable to infectious disease outbreaks are identified. The results suggest that difference in the differential outcomes in well-being is an outcome of the sanitation infrastructure inequalities and lack of sanitation infrastructure creates doubly disadvantaged populations at risk of poor hygiene and cut off from the early-warning benefits of conventional WBE. This is the first study to explore the feasibility and potential barriers to the use of WBE for tracking the attainment of SDGs globally with at least 9 out of 17 SDGs.

1. Introduction

Wastewater-based epidemiology (WBE) is a comprehensive, cost-effective, and rapid technique that can provide essential qualitative or quantitative information on residents' health and behavior within a given wastewater catchment area via the detection of urinary and fecal markers in composited municipal sewage. The currently practiced routine tracking of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and illicit drugs in wastewater by contemporary WBE (Bowes et al., 2021; Peccia et al., 2020) was preceded by pioneering work on typhoid fever in Ireland and England in the 1920s (Gray, 1929; Wilson, 1928) and poliomyelitic viruses in the United States of America (U.S.) in 1939 (Paul et al., 1939). Today, WBE is applied much more broadly for assessing the usage of pharmaceuticals and personal care products, illicit drugs, tobacco, and alcohol intake, as well as for determining exposure to and excretion of a spectrum of infectious disease agents, antibiotic resistance genes, industrial chemicals, endogenous hormones and biomarkers of nutritional status (Daughton C G and Ternes T A, 1999; Zuccato et al., 2000; Chen et al., 2019; Zhang et al., 2019; Bijlsma et al., 2020).

Tracking of SARS-CoV-2 and its variants has emerged as the most popular application of WBE globally performed by entities including national and state governments, nongovernmental organizations, universities, and commercial ventures (Daughton, 2020; Hart and Halden, 2020). Since the first literature-reported detection of SARS-CoV-2 in the Netherlands in March 2020 (Medema et al., 2020), laboratories in some 55 countries have successfully applied WBE to track the spread of COVID-19 ("COVID-19 WBE Collaborative Dashboard," 2020).

An expanded use of WBE to monitor global health is highly desirable but may be limited by a lack of centralized sewage collection and

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treatment infrastructure from which to draw composited samples that are representative of the health status of local populations around the globe (Venkatesan et al., 2015). Indeed, no global inventory of wastewater infrastructure is currently available. Some prior studies accumulated limited information collected for the purpose of assessing infrastructure impacts on sanitation and hygiene (Naik and Stenstrom, 2012) or agriculture (Sato et al., 2013). Whereas no global inventory of centralized wastewater infrastructure exists to date, this information could be particularly useful for lower income countries, which stand to benefit most from inexpensive population health assessment in settings where traditional healthcare is lacking or financially unattainable by the majority of local people.

Use of WBE potentially also could be leveraged to monitor progress in global sustainable development. With the rapid urbanization and evidence of climate change, the member countries of the United Nations (UN) have unanimously agreed on agendas for attaining sustainable social, economic, and environmental development milestones. With a target date of 2030, these agendas comprise 17 different sustainable development goals (SDGs). Some earlier studies worked on developing the framework to correlate wastewater infrastructure and sewage treatment to inform the status of the SDGs (Delanka-Pedige et al., 2021; Kanchanamala Delanka-Pedige et al., 2021; Malik et al., 2015). Building on these efforts, this study is the first to explore the feasibility and potential barriers to the use of WBE for tracking the attainment of SDGs globally.

Here, we compile and analyze existing data to (i) inventory the totality of centralized wastewater infrastructure globally, (ii) identify countries featuring and lacking such infrastructure, (iii) determine the fraction of the global population that is readily accessible to conventional WBE that leverages centralized sewerage infrastructure, (iv) rank countries based on income level (as per UN's' classification system) and on other factors to identify geographic regions which could benefit most from infrastructure improvements, and we (v) compile an initial list of wastewater-borne markers that hold promise for tracking attainment of UN SDGs.

2. Materials and methods

2.1. Literature search and data extraction

FAO's database, Web of Science, Science Direct, PubMed, and Google Scholar were used to find the number of wastewater treatment plants and the percentage of the people connected to municipal wastewater treatment plants in respective countries from 2013 using the Preferred Reporting Items for Systematic and Meta-Analysis (PRISMA) framework. One author of the team performed the initial screening and later replicated by a non-author of the team to confirm validity. Key phrase search criteria included "Municipal wastewater treatment plants in *," "People connected with treatment plants in *," "Number of centralized wastewater treatment plants in *," "people connected with centralized treatment plants in *," where * refers to each country listed in the UN. The search results were weighted by titles, abstracts, tables, and figures to determine the relevance of this study. We included journal articles focusing on municipal wastewater treatment plants, wastewater-based epidemiology. All the sources of the data and indicators with the available data are shown in Fig. 1.

An illustrative spectrum of markers was identified relying most on the very recent literature search that could potentially respond to tracking the SDGs including more than 25 different groups (Table 1), use case analysis were selected relying mostly on the very recent literature. To further assess the use of these wastewater treatment plants (WWTPs) infrastructure data, a case use analysis was performed with these data and other available health metrics. World Health Organization published a list of 100 core health indicators for health status, risk factors, service coverage, and health systems in 2015 ("Indicator Metadata Registry Details," n.d.). Six different economic, social, environmental parameters were chosen based on availability and suitability, including *Gross Domestic Product (GDP) per capita, Disability-adjusted life years*

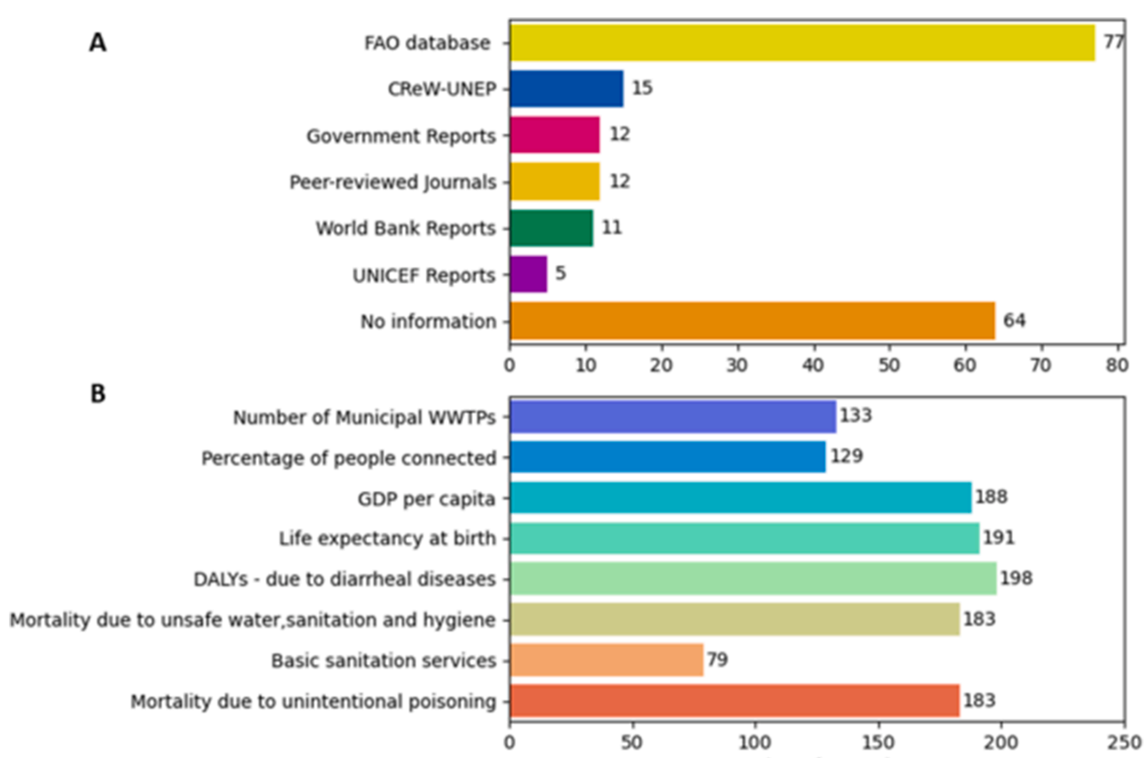

Fig. 1. Horizontal bar plot showing (**A**) the number of countries represented from each source of data, (**B**) available data on a number of countries for each socio-economic and health indicator used in this study.

Table 1
Summary of sustainable development goal agendas and the corresponding indicators proposed here for tracking using wastewater-based epidemiology.

SDGs 2030 agendas for sustainable development	Goal attributes	Proposed progress tracking using WBE
2.1.1	Prevalence of undernourishment	Endogenous biomarkers of starvation (For e.g., hunger hormones)
3.3.2	Tuberculosis incidence	Quantification of *Mycobacterium tuberculosis*
3.3.3	Malaria incidence	Quantification of *Plasmodium* parasites
3.4.1	Mortality rate attributed to cardiovascular disease, cancer, diabetes, or chronic respiratory disease	Endogenous and Exogeneous biomarkers related to heart diseases, pulmonary difficulties and cancer-causing peptides
3.4.2	Suicide mortality rate	Stress metabolites and psychotropic drugs as proxies of vulnerabilities
3.5.1	Coverage of treatment interventions (pharmacological, psychosocial and rehabilitation and aftercare services) for substance use disorders	Study of consumption of illicit and prescribed psychotropic drugs
3.5.2	Limit the uses of the alcohol per capita consumption	Alcohol related chemical biomarkers (E.g., Ethyl Sulfate)
3.9.1	Mortality rate attributed to household and ambient air pollution	Metabolites of volatile organic compounds as vulnerabilities
3.9.2	Mortality rate attributed to unsafe water, unsafe sanitation and lack of hygiene (exposure to unsafe Water, Sanitation and Hygiene for All (WASH) services)	Tracking susceptibility by quantifying pathogens and related prescribed drugs and biomarkers
3.9.3	Mortality rate attributed to unintentional poisoning	Environmental toxins (For e.g. Arsenic)
3.a.1	Limit the use of the tobacco and tobacco-related products	Nicotine-related metabolites (for e.g. cotinine, nornicotine etc.)
3.b.1	Percentage of the vaccination people in national program	Measuring vulnerabilities of unvaccinated population through biomarker assessment
3.d.2	Percentage of bloodstream infections due to selected antimicrobial-resistant organisms	Drug resistant pathogens and antimicrobial resistant genes
6.2.1	Access to basic sanitation facility with soap and water	Assessment of personal care products (For e.g. Surfactants) s
6.3.1	Improve the quality of the domestic and industrial wastewater flow	Biological Oxygen Demand, Nitrogenous Oxygen Demand etc.
8.4.1	Percentage of material footprint, material footprint per capita, and material footprint per GDP	Quantification of certain materials
9.5.1	Research and development expenditure as a proportion of GDP	Implementation of WBE demands investment in the research laboratories and manpower.
9.5.2	Researchers per million inhabitants	Different applications of WBE increase the inflow of researchers from transdisciplinary field.
9.a.1	Total official international support	Research related to WBE expands the research dimensions and ultimately brings support from international collaboration.
11.6.1	Improve the management of municipal solid waste collected and managed in controlled facilities out of total municipal waste generated, by cities	Data on type of wastewater treatment system
12.4.2	Documentation on (*a*) Hazardous waste generated per capita; and (*b*) proportion of hazardous waste treated, by type of treatment	Quantification of chemical suites of hazardous materials
14.1.1	Control the plastic debris density	Identification and relative quantification of plastics
16.1.1	Number of victims of intentional homicide per 100,000 population, by sex and age	Quantification of endogenous mental health markers as proxies of vulnerabilities

attributed to diarrheal disease due to sanitation (DALYs- diarrheal diseases), mortality rate attributed to unsafe water, sanitation, and hygiene services (Mortality - sanitation), life expectancy at birth, mortality rate to attributed to unintentional poisoning (Mortality - unintentional poisoning), and people with least basic sanitation (Least basic sanitation). Details and definitions are included in Table S1. All the countries with available data for all the parameters were categorized as 'High-Income Countries,' 'Upper-Middle Income Countries,' 'Lower-Middle Income Countries', and 'Low-Income Countries' following World Economic Situation and Prospects prepared by Development Policy and Analysis Division of the Department of Economic Social Affairs of the United Nations Secretariat. The detailed list and classification is presented in Table S2.

2.2. Statistical analyses and data visualization

Peer-reviewed articles which did not present data on the number of wastewater treatment plants within the manuscript or supplementary information were omitted from the analysis. All the databases and peer-reviewed journals were considered for this study if published in the English language. All available data was compiled in Microsoft Excel and analyzed using Python 3.8. Figures were created using a combination of Python 3.8 using Pycharm 2020.3 (Integrated Development Environment by JetBrains), ArcGIS-Pro 2.7.0, and Microsoft's Office Suite programs. Analyses were performed in Python version 3.8 using Pycharm 2020.3 (Integrated Development Environment by JetBrains). A pairwise correlation was performed on relevant infrastructure, economic, social, and environmental parameters categorically based on income level.

3. Results

From available literature sources in the English language, some 109,159 wastewater treatment plants (WWTPs) globally were identified, representing 129 countries or 67% of all nations worldwide (Table S3). These plants receive biomarker-laden wastewater from approximately 2.7 billion people, which is equivalent to 34.7% of the world's 2021 population (Fig. 2; Panels A and B).

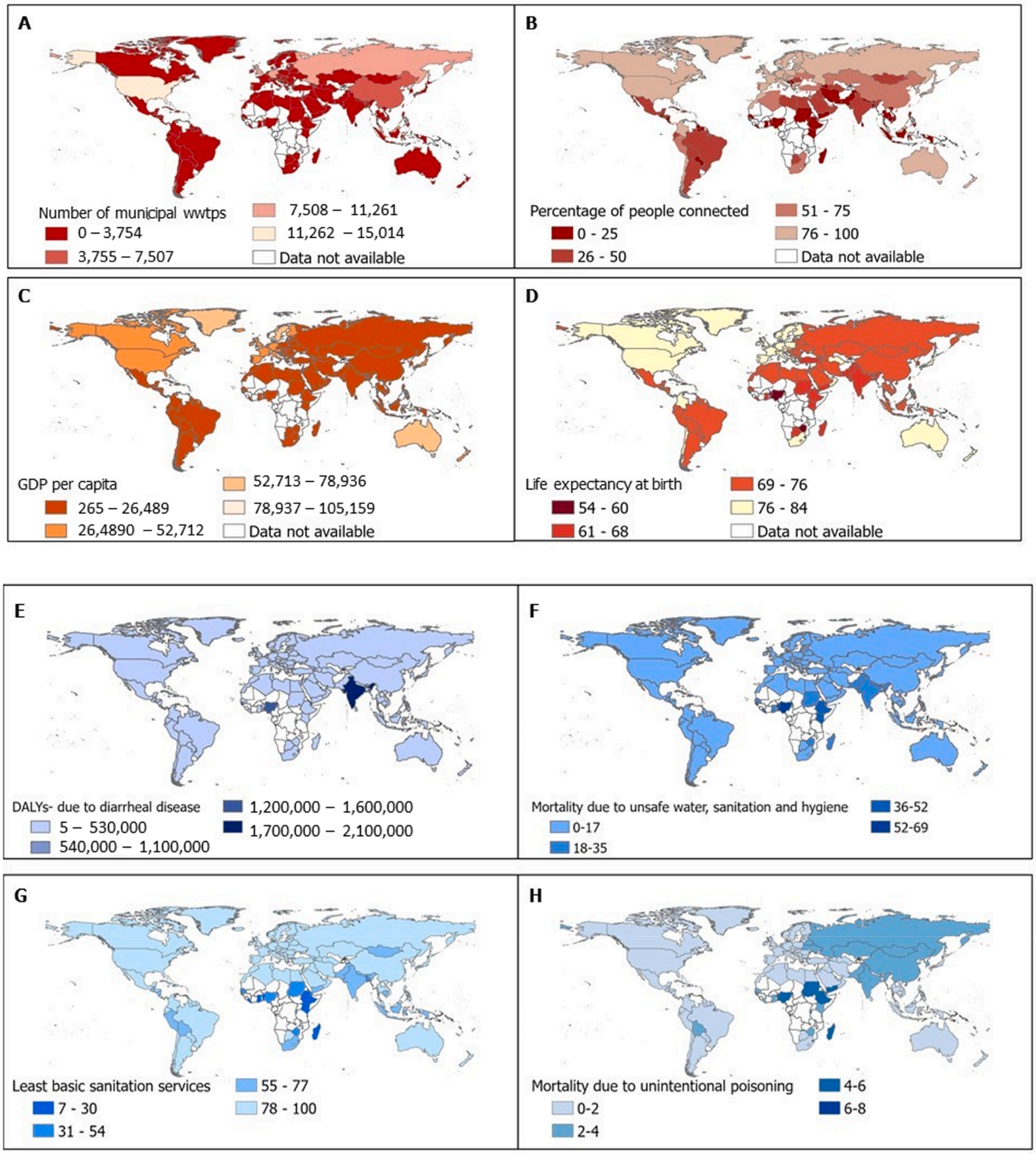

Fig. 2. Visual representation of the coverage of (A) number of municipal wastewater treatment plants (number), (B) people served by centralized wastewater treatment plants (percentage), (C) GDP per capita (US dollars per person), (D) life expectancy at birth (years), (E) DALYs - attributed to diarrheal diseases (years per thousand), (F) mortality due to unsafe water, sanitation and hygiene (number per million), (G) least basic sanitation services (percentage) and (H) mortality rate due to unintentional poisoning (number per million).

We found that in high-income countries, about 80% of the people typically are connected to and served by municipal WWTPs, with the remaining 20% either using septic tanks or lacking sewage treatment infrastructure. Thirteen countries, including Austria, Chile, Denmark, Finland, France, Germany, Kuwait, Latvia, Malta, Netherlands, Singapore, Sweden, and Switzerland, have achieved complete or near-complete (~100%) connectivity of their residents to some form of engineered centralized sewage treatment. For some 60 countries (Fig. 2; Panel A), data extraction was difficult due to a lack of information sources in the English language, resulting in poor geospatial coverage of Africa. Among those nations for which treatment infrastructure data was available (Antigua and Barbuda, the Bahamas, Barbados, Oman, Saudi Arabia, Saint Vincent and the Grenadines Seychelles, and Trinidad and Tobago), half the population or less are served by centralized wastewater systems. Notably, for Antigua and Barbuda, a nation classified in the high-income bracket, available data indicates complete absence of centralized municipal wastewater treatment (Song, 2021). In upper-middle income countries, we found only 43% of the people to be connected to centralized wastewater treatment infrastructure. Among this economic bracket of nations, Colombia has the most people connected to centralized sewage collection and treatment, whereas existing infrastructure in Bosnia and Herzegovina and in Albania only reaches about 9% of the respective populations. However, the range of values determined for the Balkan region showed a notable spread, ranging from 4% to 91%. In lower-income countries, on average about 24% of people are being served by centralized wastewater treatment systems (Fig. 2; Panel B). Eight percent of Moroccans are served by centralized sewage treatment, whereas only 3% of the population of El Salvador and Yemen enjoy this privilege. In low-income countries, as defined by the United Nations, an average of only 4% of people are served by centralized wastewater treatment, with Ethiopia ranking at the top of this group with a value of 19% (Table S3). For Haiti, not a single centralized wastewater treatment facility was documented. Most nations not included in this study (due to a lack of data) fall into the category of low-income and low-middle income countries.

Although the United States has the largest number of WWTPs (15,014) by nation, the coverage of those plants (221 WWTPs per 1 million people) is moderate (76% of total US population), ranking 11th globally (Seiple et al., 2017). By comparison, in China, which is similar in size by area, a lesser total of 4,287 WWTPs was found, placing this nation at rank #6 globally by total facility count (Qu et al., 2019); while the number of facilities is only a third of that in the U.S., China's infrastructure treats the sewage of more residents than the U.S. does, but still reaches only about 52% of its people (3 WWTPs per 1 million people), leading to a low rank of 82 globally. Most of the countries in Africa and South Asia rely on septic tanks (Irving-Bell et al., 1987; Qadeer, 2000; Polo et al., 2020), which do not readily lend themselves to the application of cost-effective, conventional WBE. Most rural areas in high-income and upper-middle-income countries also use septic systems, and information required for ranking often was not available. In the United States, as in other parts of the world, the transition of rural populations into urban ones has brought a shift from an emphasis on decentralized to centralized sewage treatment systems.

A Spearman correlation analysis was conducted to produce the heatmap shown in Fig. S1, which relates access to centralized sewage collection and treatment to geography based on the income level. The corresponding Spearman correlation coefficients are tabulated in Table S4. People's access to centralized treatment of human waste was moderately related to GDP per capita ($\rho = 0.5$) in high-income countries. In contrast, in low-middle income countries, a weaker correlation with national GDP was found ($\rho = 0.2$). *GDP per capita* (Fig. 2; Panel C) and access to centralized sewage treatment showed an even weaker, negative correlation ($\rho =$ -0.04) in low-income countries. As income levels decrease, it was found that the correlation coefficient (ρ) was decreasing, which may indicate that well-to-do people in high-income countries may prefer to live in rural areas, whereas the urban poor may have access to wastewater treatment, while otherwise being more disadvantaged. A lack of data on as-built infrastructure does not allow one to readily determine whether households in middle-low income and low-income countries use either a decentralized system for wastewater management or release human waste into the environment without any pre-treatment (Necibi et al., 2021; Singh and Suthar, 2021). Life expectancy at birth showed a moderate correlation with connectivity to municipal sewage treatment. The correlation between *life expectancy at birth* (Fig. 2; Panel D) and connectivity to WWTPs was moderate in high-income countries and even weaker in higher and lower-middle-income countries, respectively. It suggests that connectivity to centralized wastewater treatment is not indicative of life expectancy at birth. The availability of health care resources, availability of pharmaceutical products, skilled health care personnel, and life-related factors like consumption of alcohol and tobacco, and dietary habits like intake of sugar, caffeine, etc., mainly affect the life expectancy at birth (Hitiris and Posnett, 1992; Joumard et al., 2010; Martín Cervantes et al., 2019). *DALYs due to diarrheal diseases* (Fig. 2; Panel E) and service by centralized WWTPs showed a strong positive correlation in these countries ($\rho =$ 0.6).

Our analysis demonstrates (Fig. S1) that indicators of sanitation are helpful in understanding and predicting disease incidence. Specifically, we observed that the burden of disease shows a negative correlation (-0.4 $\leq \rho \leq$ -0.04) with service by centralized wastewater infrastructure. This study used *DALYs resulting from diarrheal diseases* as an indicator to describe the burden of disease in the group of countries classified based on income. In high-income countries, it showed a weaker correlation between wastewater infrastructure and disease burden, possibly explainable by the use of decentralized sewage treatment and house latrines. A similar situation was observed in the group of upper-middle-income countries.

In the category of upper-middle income countries, the correlation between WWTP infrastructure and *mortality-sanitation* (Fig. 2; Panel F) was similar to that found for high-income countries. Botswana had a higher mortality from lack of sanitation (1.8/1000 people), whereas most of the countries in upper-middle income countries had a low mortality rate (0.1/1000 people). Data on mortality in the context of centralized wastewater treatment are rare or completely unavailable in lower-middle income countries and low-income countries, due in part to the use of decentralized systems. In general, a strong correlation between existing wastewater treatment plants and mortality from lack of sanitation was observed in lower-middle-income and low-income countries. The Spearman correlation was negative between access to centralized wastewater treatment and the *mortality-sanitation* for the category of lower-middle-income countries, thereby emphasizing the need of infrastructure investments to prevent the death caused by diseases from unsafe sanitation and hygiene. For example, this principally means that connectivity to wastewater treatment alone cannot explain the mortality due to sanitation, as inadequate drinking water, hand hygiene, and microbial community exposure are additional factors that contribute to the death of people from poor sanitation (Prüss-Ustün et al., 2014; Prüss-Ustün et al., 2019; Gwenzi, 2021). In the category of low-income countries, it is evident that lack of centralized wastewater treatment shows a significant association with *mortality- sanitation*, and infrastructure investments in this region of the world are expected to translate into avoidance of deaths and extension of the lives of hundreds of thousands of people.

Among the 17 different sustainable development goals listed by the UN 2030 agenda, more than half of these may be monitored by using WBE monitoring at centralized treatment infrastructure. The 9 different SDGs identified include: SDG#2 which aims to "end hunger, achieve food security and improved nutrition and promote sustainable agriculture", SDG #3 to "ensure healthy lives and promote well-being for at all ages", SDG #6 to "ensure availability and sustainable management of water and sanitation for all", SDG #8 to "promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all", SDG #9 to "build resilient infrastructure, promote inclusive sustainable industrialization and foster innovation", SDG #11 to "make cities and human settlements inclusive, safe, resilient and sustainable", SDG #12 "ensure sustainable consumption and production patterns", SDG #14 "conserve and sustainably use the oceans, seas and marine resources for sustainable development", and SDG #16 "promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels".

We by reviewing the literature from years 2005 to 2021, we identified 25 different classes of endogenous and exogeneous biomarkers as shown in Table 1, that may prove helpful in tracking progress towards the attainment of the SDGs. These biomarkers include hunger hormones (e.g., ghrelin) (Eslami et al., 2016), stress hormones (e.g., cortisone, cortisol) (Thai et al., 2019), endogenous and exogeneous biomarkers related to cardiovascular diseases (e.g., proteinuria, collagen fragments) (Morse et al., 1979), pulmonary diseases (e.g., desmosine) (Daughton, 2018; Luisetti et al., 2008), cancer (e.g., psoriasin, lipocalin-2 nucleosides, etc.) (Rice and Kasprzyk-Hordern, 2019), different classes of illicit drugs (e.g., fentanyl, heroin, cocaine etc.) (Barceló, 2020; Choi et al., 2018; Gushgari et al., 2018; Senta et al., 2020), personal care products (e.g., parabens, triclosan, microbeads) (Heidler et al., 2006; Kumar et al., 2019; Senta et al., 2020) and surfactants (e.g., benzalkonium chloride, benzethonium chloride etc.) (Alygizakis et al., 2021), hazardous chemicals (e.g., arsenic, benzene, lead, mercury) (Muhammad-aree and Teepoo, 2020), drug resistant pathogens (Sims and Kasprzyk-Hordern, 2020), antimicrobial resistant genes and psychotropic drugs (e.g., alprazolam, tricyclic antidepressants, Z-drugs, NPS etc.) (Bade et al., 2022). All of these biosignatures may provide value for tracking progress in attaining the UN SDGs".

4. Discussion

Developed over the past two decades, WBE is quickly becoming the preferred diagnostic tool to monitor community spread of COVID-19 (Balboa et al., 2021; Fontenele et al., 2021; Nemudryi et al., 2020; Sherchan et al., 2020; Westhaus et al., 2021), thereby raising the prospect of reaping additional benefits from this technology, including tracking of sustainable development globally. At the onset of the pandemic, conventional and individualized clinical testing was overwhelmed due to both limited resources and limited healthcare infrastructure. This provided an opening for WBE to position this nascent technology as one of the prominent supplement tools for assessing spread of the virus and using its detection and abundance as an early indicator for new cases, morbidity, and mortality to surge (Wu et al., 2020). In addition, WBE was used to detect the virus in communities where clinical evidence for the presence of virus was absent (Bowes et al., 2021). The present analysis was conducted in part to assess the potential global reach of WBE for helping to inform national and state governments in their response to the COVID-19 pandemic. The diagnostic value of wastewater is not limited to the new coronavirus; however, the data presented here can be used to inform public health tracking and intervention placement for a spectrum of diseases and health threats. Results show that monitoring even just half of the world's population cannot be simply achieved by performing WBE analyses on all existing centralized sewerage systems documented worldwide. Such a global effort would reach only about a third of the global population. Our analysis shows that economic and health disparities extend to access to WBE. Only about 66 countries globally have English-language documented centralized infrastructure in place to monitor at least one-half of the population by WBE; whereas this could be leveraged to address the COVID-19 pandemic and other public health priorities, benefactors would be mainly high-income and middle-income countries. As expected, access to sanitation infrastructure helps to lower mortality rates, as is evident in high-income countries. Access to sanitation infrastructure limits fecal contamination and spread of waterborne diseases, with case studies reaching as far back as outbreaks in the 1880s (Kesztenbaum and Rosenthal, 2017). In this setting, about 80% of the people are served by wastewater treatment facilities and an additional 15% of the people are connected to decentralized systems, thereby fostering a reduced mortality. Some countries like Antigua and Barbuda and Saint Vincent and the Grenadines are behind in implementing sanitation services despite having a relatively high national income (Haller et al., 2007; Irazábal, 2021).

Conversely, lower income nations find themselves in a situation of double disadvantage. In low-income countries, the correlation of disease burden and WWTP infrastructure suggests an importance of the fecal-oral route for disease propagation (Fuente et al., 2020). Access to water and sanitation is a basic human right (United Nations General Assembly 2010) rather than a privilege. However, many low-income or lower-middle-income and even upper-middle-income countries do not have access to proper hygiene and sanitation. The World Health Organization and the United Nations Children's Fund Joint Monitoring Programme both define sanitation as disposing of human excreta using appropriately engineered facilities. Indeed the SDGs call out improved sanitation as an ideal indicator for the progress of human wellbeing (Malik et al., 2015). However, poor sanitation continues to exist around the world, and lack of wastewater infrastructure can help to explain the excess mortality observed due to preventable diseases in the world. Lack of centralized infrastructure renders populations vulnerable to an elevated risk of infectious disease outbreaks and transmission, while monitoring and detecting the same is difficult due to a lack of access to composited human waste for convenient population health monitoring using WBE.

Similarly, the tracking of harmful exposures to other agents, such as chemical toxins and contaminants of emerging concern (CECs), is made difficult in developing countries due to the lack of centralized treatment plants that can serve as chemical observatories to identified and quantify mass loadings of pollutants via analysis of WWTP influent and effluent (Venkatesan and Halden, 2014). A lack of wastewater infrastructure prevents researchers from generating information which health authorities require to know when and where to take action. Wastewater treatment plants have long been considered an integral part of the safety of aquatic ecosystems and human health (Daigger et al., 2017). Nations like the USA in the past have made significant investments into centralized treatment of human waste. However, past investments are no guarantee for present-day ecosystem integrity and human health protection. Inadequate maintenance of existing systems in 2017 earned the USA a dismal rating of D + for its wastewater infrastructure (ASCE, 2017). And yet, the condition of wastewater infrastructure in other parts of the world, especially in South Asia, Central Asia, and Africa, is even worse than that of the USA (Karthe et al., 2017; Lorenzo and Kinzig, 2019; Wang et al., 2014). Rapid urbanization in these locales demands investments into the construction of more wastewater infrastructure; yet, a lack of economic stature, political stability and forward-looking planning is placing millions of people in jeopardy. In contrast, countries belonging to the European Union have acknowledged and invested in the need for state-of-the-art wastewater collection and treatment infrastructure over the past decade, which is reflected in the fact that nearly the entire population of these countries is served by centralized treatment plants (>98%).

In constructing the database presented here, several challenges were encountered in estimating the number of WWTPs globally, beginning with the basic challenge of defining the term "wastewater treatment plant." Since most of the literature follows the definition of the United Nation's Food and Agricultural Organization (FAO) (Naik and Stenstrom, 2012; Sato et al., 2013; Malik et al., 2015), we elected to also adopt their definition. In addition, the definition of the wastewater differs from country to country depending upon the federal rule on sewerage system. For example: all the household in France are required by law to be connected to either communal network of collective sanitation or a recovery by non-collective sanitation equipment within a small collection system. About 21,000 such systems are operated today and about 3275 only fall under the definition of FAO serving more than 20,000 inhabitants as forementioned. The numbers presented in this study is a conservative estimation of the global centralized network within the order of magnitude rather than absolute value to further gauge in discussions to benefit people from inexpensive health assessment through WBE. Further challenges arose from the need to distinguish between municipal and industrial treatment infrastructure and from incomplete data on the number of people served by these facilities. Geographical differences in data availability were readily apparent and particularly pronounced for the African continent for all data categories. Although not essential for the purpose of WBE, information also was limited concerning the type of treatment and the treatment efficiency of existing plants. In most of the countries, information on the number and types of treatment stages was not available. It should be noted that the proposed markers are illustrative rather than comprehensive. There are new ones to be discovered, as well as existing ones that need to be validated.

The use of the WBE is not restricted necessarily to locations where centralized wastewater treatment is practiced. Some studies have demonstrated that open ponds, portable toilets, and latrines can be sampled to yield meaningful public health information (Knappett et al., 2011). While such pioneering work can be helpful to study public health conditions during special events and natural or human-caused disasters (e.g., war refugee camps), the greatest economy of WBE results from measuring non-attenuating markers at large WWTPs (Hart and Halden, 2020). Overall, today most nations are only scratching the surface of all the benefits that may be derived from WBE. Research efforts are ongoing to expand existing applications in locations other than centralized wastewater treatment infrastructure and new markers of human behavior, health, sustainability, and wellbeing (Choi et al., 2020). For instance, cardiovascular diseases and pulmonary diseases account for 20 million deaths annually and for about 35% of all mortality in developing and developed nations alike (Gavazzi et al., 2004). This challenges the biomedical research community to expand WBE for tracking of these major killers by identifying exogenous and endogenous biomarkers of disease. Different classes of biomarkers relate to human behavior, lifestyle, and human health on a community-level. Measurements made can be normalized and reported on a per-capita basis. Some 25 different classes of markers that can be leveraged to achieve various SDGs have been identified here. Some of these proposed markers have not been explored or validated yet, while other have and are widely used in WBE. Various protein biomarkers, markers of food and diet, volatile organic compounds, antibiotic resistance genes and microbiomes alongside the biomarkers pertaining to non-communicable diseases like cardiovascular and cancers, have been proposed in the literature; these may be leveraged to attain the objectives of SDGs (Choi et al., 2020, 2018; Faleye et al., 2021; McGraw et al., 2021; Rice and Kasprzyk-Hordern, 2019).

The database on centralized sewage treatment compiled here (Table S3) can serve as a first approximation of the number and locations of WWTPs globally and of the populations served by this infrastructure that are readily accessible to WBE. Future use of a consensus definitions of sewage infrastructure would be helpful in addressing remaining data gaps. The concept of WBE do require the expertise of handling large datasets and trained professionals. Various chemical nature of markers including standardized metabolite excretion rates, degradation rates and stability of markers with respect to pH and temperature has to be considered requiring competent professionals before employing WBE to track attainment of SDGs. In addition, the current applications of WBE with respect to the small molecular markers require expensive instruments like liquid chromatography tandem mass spectrometry and reverse transcription polymerase chain reaction (RT-PCR). However, there are numerous examples of using inexpensive environmentally friendly immuno-assay and paper-based sensors to detect infectious diseases and chemical compounds. For example, Zika's paper microchip and Malaria's paper microfluidic device has been employed in the past in resource-constrained regions as complementary tool to WBE (Jiménez-Rodríguez et al., 2022).

Our analysis shows the significant potential of using WBE with an expansive list of markers (Table 1) to track attainment of SDGs. These UN goals have been linked with each other and are interdependent (Delanka-Pedige et al., 2021). The development of the affordable and sustainable wastewater infrastructure (SDG #6 and 9) may unlock the applications of WBE, which then could provide a vantage point to understand the overall health of the community (SDG #11) in real-time through monitoring of human metabolites of interest, mental health ~~bio~~markers, infectious diseases (SDG #2, 3, 8, 12, 14 and 16) and to intervene accordingly, using the data generated from this innovative technology that is responsive to 20 objectives from those goals (Table 1).

5. Conclusion

Among individuals privileged by having access to sanitation infrastructure, 67% or 3 billion are being served by centralized wastewater treatment plants. However, the goal of reaching these populations is still elusive. Whereas WBE use has been reported for some 3,000 sites globally, the corresponding population count is small to what is theoretically is possible. The current lack of sanitation infrastructure is hampering progress in both understanding and preventing the spread of infectious diseases. The Covid-19 pandemic has already triggered significant investments in an enhancement of infrastructure and health surveillance tools. The pandemic further has illustrated that WBE can be leveraged to identify the epicenter of infectious diseases more quickly than clinical testing can, thereby providing an avenue for preventing diseases and minimizing economic hardship in both developing and developed nations partaking in global commerce. Indeed, the Covid-19 pandemic serves as a powerful illustration of the benefits of conducting multidisciplinary WBE research to detect, manage, and prevent current and future outbreaks of infectious disease. Aside from better responding to the threat of infectious diseases, WBE also opens the doors for enhanced management of chemical risks. Threat agents of concern include organophosphates, microplastics, endocrine disruptors and a spectrum of traditional and emerging contaminants of concern. In addition to managing biological and chemical risks, WBE further can provide a potentially inexpensive and practical tool for monitoring dietary intake and dietary deficiencies in populations around the world and for the study of endogenous biomarkers, such as stress hormones that may provide insights into human wellbeing and quality of life.

The buildout of sanitation infrastructure is key for protecting human health and critical ecosystems alike. Decisions on the type of infrastructure to be implemented are location-specific. Opting for a centralized treatment infrastructure brings the added benefit of enabling real-time observation of population health through the implementation of WBE. The use of WBE in decentralized, small sewerage systems is a possible option but comes at the expense of a reduced economy of scale. Expanding the use of WBE in the future is feasible and desirable, with data from this study indicating opportunities for tracking in real-time the progress made in attaining global health and the sustainable development goals formulated by the United Nations.

CRediT authorship contribution statement

Sangeet Adhikari: Conceptualization, Methodology, Formal analysis, Visualization, Writing – original draft. **Rolf U. Halden:** Conceptualization, Supervision, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

RUH is founder of the nonprofit proejct, OneWaterOneHealth, of the Arizona State University Foundation and founding member of AquaVitas, LLC, a startup company of Arizona State University.

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Appendix A. Supplementary data

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