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Title: Wastewater Surveillance for Infectious Disease: A Systematic Review

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Abbreviations: PRISMA, preferred reporting items for systematic reviews and meta-analyses; WW, wastewater;

Abstract:

Wastewater surveillance of SARS-CoV-2 has been shown to be a valuable source of information regarding SARS-CoV-2 transmission and COVID-19 cases. Though the method has been used for several decades to track other infectious diseases, there has not been a comprehensive review outlining all of the pathogens that have been surveilled through wastewater. Herein we identify what infectious diseases have been previously studied via wastewater surveillance prior to the COVID-19 pandemic. Infectious diseases and pathogens were identified in 100 studies of wastewater surveillance across 38 countries, as well as themes of how wastewater surveillance and other measures of disease transmission were linked. Twenty-five separate pathogen families were identified in the included studies, with the majority of studies examining pathogens from the family Picornaviridae, including polio and non-polio enteroviruses. Most studies of wastewater surveillance did not link what was found in the wastewater to other measures of disease transmission. Among those studies that did, the value reported varied by study. Wastewater surveillance should be considered as a potential tool for many infectious diseases. Wastewater surveillance studies can be improved by incorporating other measures of disease transmission at the population-level including disease incidence and hospitalizations.

Introduction:

Infectious disease surveillance is most commonly conducted at the health center or the hospital (1), either through passive reporting or active case identification (2). This type of clinical surveillance requires events, where the event of a case, hospitalization, or death occurring allows for estimations in trends in morbidity and mortality (Figure 1). In this way, the number of cases, hospitalizations, and deaths from endemic infectious diseases such as malaria or influenza are tracked and the effectiveness of interventions such as mosquito control or vaccines can be monitored. Importantly, due to cost and unequal access to clinical healthcare diagnostic tools, many pathogens under surveillance are characterized by their symptoms or syndromes, such as influenza-like illness. For emerging pathogens, event-based infectious disease surveillance may note an unexpected increase in some symptom or condition, notably as occurred with microcephaly and Zika (3,4), or observed pneumonia cases without a known cause as occurred with COVID-19 (5). Event-based infectious disease surveillance requires a health system capable of observing trends, a population with sufficient access to that health system, and a sufficiently large trend or cluster of odd cases to alert officials. Importantly, event-based surveillance misses any infectious disease transmission that is not captured by cases, hospitalizations, and deaths (Figure 1).

Environmental surveillance, on the other hand, is a broad category for systems that monitor the potential risk of a pathogen by identifying and perhaps quantifying that pathogen in the environment. Their defining characteristic is the circumvention of human behavior and health systems, which reduces bias, while still providing information regarding risks to human health.

For example, environmental surveillance may routinely test known vectors for pathogens (6), alerting the public to the detection of, or an increase in, the pathogen in the vector population.

Wastewater surveillance is a type of environmental surveillance that has historically been utilized to track water-borne or fecal-orally transmitted pathogens. The origins of wastewater surveillance go back to the London cholera epidemic of the mid-1800's where John Snow, identified a cesspool near a house with multiple cholera deaths that was excavated and found to be leaking into the pump's water supply (7)**.** With the scientific evidence supporting germ theory at the time, scientists began hunting sewage not only for cholera but also for other pathogens including salmonella typhi bacteria (typhoid) (8,9), coxsackie viruses (10), and poliovirus (11). From the 1970's onward, wastewater surveillance formed a critical component of the worldwide initiative to eradicate polio (12), and perhaps polio provides the best contrast between event-based and environmental surveillance systems. Whereas event-based polio surveillance relies on an unexpected increase in acute flaccid paralysis which occurs in only 0.5% of polio cases (13), wastewater surveillance can detect poliovirus circulating in a community prior to widespread transmission (14).

In general, wastewater surveillance provides an indicator of infectious disease transmission independent of treatment-seeking behavior or access to care. It is most easily implemented at a wastewater treatment plant, which provides a representative sample for all individuals connected to the sewer network. The approach can also be implemented upstream from a wastewater treatment plant or even in communities without a wastewater treatment plant so long as sewage from multiple individuals gathers at a centralized point (septic tanks, latrines, and lack of sanitation access present challenges to wastewater surveillance systems). By circumventing the need for a diagnostic test, wastewater surveillance better captures the spectrum in infectious diseases including asymptomatic infections and cases that may not seek treatment (Figure 1). Care and expertise are needed to interpret the results from wastewater surveillance, as fecal or urinary shedding rates and timing of different pathogens varies. Indeed, perhaps the greatest amount of research advance that is needed is in relating what is found in wastewater surveillance back to public health understanding and action.

The COVID-19 pandemic saw the broad adaptation of wastewater surveillance across the globe (15), as the limitations of event-based surveillance systems for an emerging pathogen were laid bare. Most interestingly, COVID-19 is a respiratory-transmitted pathogen, suggesting that a pathogen's mode of transmission need not be fecal-oral or waterborne for wastewater surveillance to be useful. Recent reviews of wastewater detection focusing on COVID-19 have elaborated on the importance of this method for detecting viruses with specific focus on pathogens transmitted via the fecal-oral route despite COVID-19 being a respiratory virus (16). This focus suggests a potential gap in knowledge for wastewater-based epidemiology where the assumed scope of pathogens for this method may be limited by researchers' perception that the pathogen must be transmitted through the fecal-oral or waterborne routes. Other reviews have also focused exclusively on viruses ignoring the potential for detecting bacteria in wastewater to inform public health action (17). This leads to the key questions we seek to answer: 1)What infectious diseases have been detected in wastewater and can public health systems incorporate their detection as they build capacity in wastewater surveillance?, and 2)What insights for public health can be drawn from the types of pathogens that have been detected in wastewater? Herein we present a systematic review of wastewater surveillance for infectious diseases other than COVID-19, reporting the documented successes of testing wastewater for infectious disease pathogens that circulate primarily in humans.

Methods:

Systematic Literature Review

Following PRISMA guidelines (18), we searched PubMed, SCOPUS, Science Direct and Google Scholar for studies looking at wastewater-based surveillance of infectious diseases (both viral and bacterial) in human populations and published before August 1st, 2020. For the databases (PubMed, SCOPUS, and Science Direct), search terms included Mesh headings, MeSH terms, and text words and synonyms, including “Wastewater”, “Waste water”, “Sewage”, “Sewer”, “Environmental”, “Surveillance”, “Disease”, “Feces”, "wastewater-based epidemiology", "Environmental surveillance", “Environmental Epidemiology “, “Wastewater Surveillance “, "Environmental Monitoring", "Wastewater Monitoring", “Virus”, “Bacteria”. These terms were combined using the boolean terms “AND” and “OR” when applicable. Similar terms were used but with filters on Google Scholar to limit the search to material of interest. The filters included the inclusion of the characters “doi” to look for a Digital Object Identifier to ensure that it was a published work, and the exclusion of the terms "systematic review", "literature review", "meta-analysis", and "review" in the title. The boolean term “NOT” was used to aid in excluding these terms. All sources, databases and Google Scholar, were filtered to look for texts in the English language.

Once article lists were pulled from their respective sources, duplicates were removed, using Microsoft Excel’s built-in remove duplicated function, using both title and authors as the reference for removal. Reviewers screened titles and abstracts for remaining articles, retrieved articles for full-text review, and assessed full-text articles based on eligibility criteria.

Eligibility Criteria

We included published studies which tested wastewater for communicable and/or infectious human diseases on more than one occasion and during two or more time periods. Non-communicable diseases, such as diabetes and obesity, were excluded. As we defined surveillance as having the requirement of testing over time, all articles which tested wastewater only once and/or on a single day were excluded. Articles which discussed diseases not related to humans or not in the context of humans (e.g. influenza virus in pigs), were also excluded. Peer-reviewed journal articles were included as long as they were not reviews, systematic reviews, literature reviews, or meta-analyses. Non-peer reviewed journal articles such as research notes, research letters, and short communications were excluded. Methods papers that looked purely at and compared different techniques of drawing and sampling wastewater were also excluded if they did not offer analysis of pathogens naturally present in the wastewater. This included studies that spike wastewater with a pathogen only to look at recovery in the context of comparing methods of sampling. Lastly, with the goal of understanding what else can be surveilled in wastewater we excluded all papers which reported the surveillance of SARS-CoV-2 in wastewater. Wastewater surveillance for SARS-CoV-2 has been covered by several reviews already (17,19–23). This determination was made to support the utility of environmental surveillance outside of emergency/pandemic situations, to determine what and where disease surveillance has been conducted in the past, and to support expansion and extension of wastewater surveillance to other pathogens and regions.

Data Extraction

We initially extracted the following information from the articles meeting the eligibility criteria: period of sampling, country the sampling occurred in, pathogen(s)/disease(s) being monitored, number of samples pulled, amount of sample pulled, sample type (grab, composite, other), method of detection, overall findings, was genetic typing done, and did the researchers connect their findings to population health. The primary information of interest were the disease(s) being monitored, method of detection, and if the authors connected their findings to population health.

Role of the funding source

There was no funding source for this study.

Results

Literature searches initially identified 1005 entries (after removing duplicates), of which 159 abstracts met the inclusion criteria. After review of the articles, 100 scientific papers were included (Figure 2, Table 1). More detail on each study is available in a spreadsheet format in web appendix 1.

Across the 100 included articles, studies were conducted in 38 countries with the most studies conducted in Italy (10 studies), China (8 studies), Japan (7 studies), Israel (7 studies), and Brazil (7 studies). These 5 countries accounted for 39% (39/100) of the studies conducted across all articles.

Within the included articles, the most prevalent pathogens found were viruses from the families Picornaviridae, Calciviridae, Adenoviridae, Reoviridae, and Hepeviridae (Figure 4). Of the most prevalent families, three of them are known to have pathogens contributing to diarrheal diseases (Picornaviridae, Caliciviridae, and Reoviridae) and make up 57.5% of the pathogens studied across all articles. Within the Piconaviridae family, the most prevalent genus studied was enteroviruses, with poliovirus being the most common among that genus. Enteroviruses made up 32.5% (52 instances) of pathogens found in all of the articles. Additionally, there were 20 other families of pathogens that appeared between 1 - 9 times within our literature review, with a mean of 2.2 appearances and a median of 2 appearances each. Considering the global burden of disease (Figure 5), diarrheal diseases were the most represented among studies of wastewater surveillance, with other infectious diseases with a great burden not found in this systematic review. Infectious diseases of international concern (a World Health Organization distinction (24)) were better represented, with only influenza and HIV/AIDS not represented among studies of wastewater surveillance (Figure 5).

A number of studies correlated the level of an infectious disease pathogen found in wastewater to relevant measures of transmission such as population-level incidence, without reporting if public health action or policy was influenced by wastewater surveillance or not (Figure 6). For example, studies have linked the level of norovirus in wastewater to incidence of gastroenteritis (25), levels of hepatitis E virus in wastewater to incidence of hepatitis E (26), and level of enteric viruses in wastewater to the incidence of acute diarrhea (27). Other studies compared population seroprevalence to the level of hepatitis A virus (28) and hepatitis E virus (29) found in wastewater. In comparison with the incidence of clinical cases, wastewater surveillance provided early warning of hepatitis A virus and norovirus outbreaks in Sweden (30). However, in the Netherlands wastewater surveillance did not serve well in an early warning capacity for a variety of enteroviruses (31). Wastewater surveillance correlated well with outbreaks of enterovirus (32), hepatitis A virus (33), and *Salmonella enterica* (34,35). In Russia, outbreaks of aseptic meningitis caused by echovirus type 6 correlated with levels in wastewater, but outbreaks of aseptic meningitis caused by echovirus type 30 did not (36). A few studies directly compared the sensitivity of surveillance for the incidence of acute flaccid paralysis (a type of non-specific clinical surveillance) to wastewater surveillance for poliovirus, finding that wastewater surveillance was more sensitive and combining the two systems was optimal (37–40). The most common type of comparison of wastewater surveillance with clinical cases linked the genetic diversity of bacteria or viral strains found in wastewater surveillance back to samples from clinical cases of meningitis, gastroenteritis, or diarrhea-related illness (41–62). These studies did not examine the use of wastewater surveillance to inform of outbreaks or correlate levels of the pathogens found in wastewater to trends in population-level incidence over time.

A handful of publications documented the utility of wastewater surveillance to assess the impact of public health interventions (Figure 6). Wastewater surveillance was able to confirm the cessation of the transmission of vaccine-derived poliovirus following a transition from oral poliovirus vaccine to inactivated poliovirus vaccine in numerous studies (63–66). Wastewater surveillance was also used to assess the impact of rotavirus vaccine deployment in Rio de Janeiro, Brazil (67).

When considering the use of wastewater surveillance to inform public health action or policy (Figure 6), the most common reported application was to document the elimination of wildtype poliovirus transmission (68–74). In countries with circulation of wildtype poliovirus, wastewater surveillance has been used to guide vaccination efforts. In Nigeria, directed vaccine efforts based on results from wastewater surveillance interrupted polio transmission in numerous areas (75). In Mumbai, India, wastewater surveillance was used to alert importation of wild-type poliovirus and inform subsequent vaccine distributions (76). And in Israel, the importation of wildtype poliovirus was detected using wastewater surveillance which then led to an expansion of wastewater surveillance and vaccination campaigns to prevent re-establishment of poliovirus transmission (77). No articles were identified that documented the use of wastewater surveillance to inform public health action for any other pathogen than poliovirus.

The majority of articles reporting on wastewater surveillance included no comparison to other measures of transmission such as clinical cases of disease (Figure 5). Some articles assessed the presence of poliovirus (78–81), either wildtype or vaccine-derived, including potential neurovirulence of vaccine-derived poliovirus (82–84). Many articles documented the diversity of non-polio enteroviruses found in wastewater (82,85–100), with a variety of focuses including rotavirus (101–105), norovirus (97,100,106–108), astrovirus (109,110), polyomavirus (111), Saffold virus (112), hepatitis A virus (94), hepatitis E virus (113), mastadenovirus (114), Aichi virus (115), and human bocavirus (115). Surveillance of *Giardia* and/or *Cryptosporidium* was also documented (116,117). Other studies examined the extent of antimicrobial resistance (118,119), or virulence genes (120), in *Escherichia coli* or *Salmonella* bacteria.

Discussion

Numerous pathogens have been found in wastewater, not just those transmitted via the fecal-oral route. The majority of studies, unfortunately, failed to link what was found in the wastewater to what is observed in other measures of population health , Linking wastewater surveillance to population-level health can be challenging, but this is a first key step in understanding wastewater surveillance's role in public health. Wastewater sewersheds rarely align spatially with political boundaries that are used to report infectious disease dynamics (such as counties or postal codes), and unless an infectious disease is notifiable then estimates of incidence are not likely available. Nevertheless, linking wastewater surveillance to an estimate of population-level incidence or prevalence should at least be attempted; we found relatively few studies reporting any estimate of the disease burden. There is difficulty in obtaining incidence rates for a variety of pathogens, but this should not prevent scientists from comparing wastewater surveillance to syndromic surveillance, e.g. incidence of diarrhea, gastroenteritis, or pneumonia. Increased collaboration between epidemiologists, microbiologists, and environmental engineers is needed to maximize the knowledge gained from studies of wastewater surveillance.

Furthermore, we found that wastewater surveillance has been used extensively to guide public health policy and interventions to eliminate and eradicate poliovirus, but we found no reports of wastewater surveillance being used proactively for other pathogens. With the COVID-19 pandemic, wastewater surveillance has been proactively used by a variety of organizations, including institutions of higher education (121), local health departments, and national governments (122). From our review, the most obvious link between wastewater surveillance and public health policy/intervention was the confirmation of the absence of transmission of polio, as well as early notification or confirmation of outbreaks. With the expansion of wastewater surveillance during the COVID-19 pandemic, we anticipate use of this tool in evaluating policy and intervention impact in similar ways that environmental surveillance for vector-borne diseases is used (123).

As evidenced in this review, epidemiologists have typically thought of wastewater surveillance only as a tool to surveil pathogens that are either waterborne or fecal-orally transmitted. For example, a recent textbook from the Global Pathogens Project highlights the potential for wastewater surveillance for waterborne pathogens, but completely ignores pathogens of other transmission types (https://www.waterpathogens.org/). This narrow focus overlooks the potential utility of wastewater surveillance for sexually-transmitted, respiratory-transmitted, and vector-borne diseases of pandemic potential (124,125). Indeed, only one of the six times that the World Health Organization has declared a public health emergency of international concern (a term conceptualized in 2005) has the pathogen been waterborne or fecal-orally transmitted (poliovirus compared to H1N1 influenza, ebola twice, Zika, and COVID-19) (24). In addition, the only pandemics in the 20th century were caused by influenza and HIV/AIDS.

The COVID-19 pandemic has shown wastewater surveillance to be an effective tool for a respiratory-transmitted pathogen (126). Given the low cost and population-level representation that a single wastewater sample provides, further research into the utility of wastewater surveillance for infectious diseases in general is needed. Among other pathogens that are not waterborne nor fecal-orally transmitted, we found reports of Zika and Ebola virus in wastewater, suggesting that they could be potential targets of continuous wastewater surveillance. Wastewater surveillance could be useful for other high-burden infectious diseases as well. Evidence from the 1990's suggests HIV can be detected in wastewater (127), and this systematic review found a report of HIV detection in wastewater. (It was only a single detection and so was not considered "surveillance"). Tuberculosis can also be found in wastewater (128), even to the extent of endangering sewage workers (129). But again this systematic review found no reports of surveilling tuberculosis in wastewater. Bearing in mind that wastewater surveillance is useful for tracking antimicrobial resistance (130) should wastewater be useful for surveilling tuberculosis, then it could potentially be used to surveil multi-drug resistant tuberculosis as well. Malaria can be easily diagnosed in human feces (131), which leaves us to speculate the possibility for finding and surveilling this pathogen in wastewater, perhaps again aimed toward drug-resistant malaria. Numerous groups are currently assessing the capacity to find influenza in wastewater with success now documented from Michigan (132), but H1N1 influenza was not found in the wastewater of the Netherlands during the 2009 pandemic (133). Additionally there is evidence that respiratory synctial virus may be surveilled in wastewater (134).

Wastewater surveillance should be considered a general tool for public health going forward. As with any tool, wastewater surveillance will certainly have limitations. Of course, any person not connected to a sewer network will be missed by wastewater surveillance and in many countries across the globe sewer networks are rare. Wastewater surveillance is more easily done in larger cities, but larger cities also have to deal with greater dilution of a pathogen in larger volumes of wastewater. Additionally, shedding into wastewater via urine, feces, oral secretions, or other mechanism will vary by pathogen and further understanding of different shedding rates is needed. However, the advances in wastewater surveillance for SARS-CoV-2 were not made by extensive fecal shedding studies that to this date have not been conducted. Instead, the advancements were driven by the high quantity of clinical surveillance data – COVID-19 is a notifiable disease in the US and many countries across the world and as such the incidence of COVID-19 can be easily linked to levels of SARs-CoV-2 RNA in wastewater. Numerous studies have now modeled SARS-CoV-2 transmission as a function of wastewater (135–139). Linking what is found in wastewater to population-level measures of incidence and/or prevalence for other pathogens is key to understanding how this type of surveillance information can be used for public health benefit.

The science of detecting and quantifying pathogens in wastewater has advanced rapidly through the course of the COVID-19 pandemic, but is nowhere near settled. Ensuring sound methodology in testing wastewater for pathogens is required to build confidence in the utility of the tool for public health benefit (140,141). In principle, the process involves four distinct steps: 1) sampling, 2) concentration, 3) nucleic acid extraction, and 4) nucleic acid measurement. A 24-hour composite sample is considered the gold standard for sampling. Passive sampling with Moore swabs (142) or polar organic chemical integrative samplers (143) is also viable, as is sampling with grab samples albeit at potentially reduced sensitivity (144). There is an outstanding question about whether sampling from wastewater or sludge (settled solids) is better (126). The settling process will naturally concentrate pathogen nucleic acids suggesting sludge may be more sensitive, but sludge is not easily accessed at smaller treatment plants nor upstream from treatment plants. Numerous methods have been published regarding concentration. The US Centers for Disease Control lists five approaches to concentrating SARS-CoV-2 RNA in wastewater, namely: ultrafiltration, filtration through an electronegative membrane, polyethylene glycol precipitation, skim milk flocculation, and ultracentrifugation. This is not a definitive list of methods employed for concentrating nucleic acids in wastewater, and variations within these methods also exist. While some comparison studies have been conducted for SARS-CoV-2 (145–147), it is unknown whether the different methods are more or less sensitive for different pathogens. The extraction of nucleic acids from wastewater also has a variety of methods, with numerous wastewater-specific extraction kits readily available from commercial companies.

Lastly, quantitative polymerase chain reaction (qPCR) or digital droplet PCR (ddPCR) are both used extensively for detecting and quantifying a pathogen in wastewater (148).

A variety of factors affect the probability that a pathogen will be found in wastewater and then documented in the scientific literature. Publication bias certainly plays a role, with numerous pathogens neglected in the scientific literature (149), as well as negative results not being published. Along these lines different types of studies are needed including studies of load shedding dynamics, pathogens' persistence in wastewater, and the relationship between levels of a pathogen found in wastewater and other measures of transmission such as population-level incidence. Perhaps most important for public health, more studies are needed that assess the utility of wastewater surveillance to guide policy and public health intervention.

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Table 1: Characteristics of wastewater surveillance studies included in the systematic review [a]

First Author, Year (Reference No.)	**Years of Study**	**Country**	**Population health measures**
Adenovirus			
Aw, 2010 (150)	2007 - 2007	Singapore	Yes
Bisseux, 2018 (61)	2014 - 2015	France	No
Elmahdy, 2020 (115)	2017 - 2017	Egypt	Yes
Farkas, 2018 (96)	2016 - 2017	United Kingdom (Wales)	No
Garcia, 2012 (100)	2010 - 2011	Brazil	No
Grøndahl-Rosado, 2014 (97)	2011 - 2012	Norway	Yes
Hellmér, 2014 (30)	2013 - 2013	Sweden	Yes
Kiulia, 2010 (105)	2007 - 2008	Kenya	No
Lun, 2019 (114)	2016 - 2017	Australia	Yes
McCall, 2020 (60)	2017 - 2018	United States of America	No
O'Brien, 2017 (98)	2016 - 2016	Uganda	No
Prevost, 2015 (27)	2013 - 2014	France	Yes
Aichi virus			
Hellmér, 2014 (30)	2013 - 2013	Sweden	Yes
Prevost, 2015 (27)	2013 - 2014	France	Yes
Shaheen, 2020 (115)	2017 - 2018	Egypt	No
Wong, 2013 (86)	2006 - 2007	United States of America	No
Astrovirus			
Aw, 2010 (150)	2007 - 2007	Singapore	Yes
Hellmér, 2014 (30)	2013 - 2013	Sweden	Yes
Kiulia, 2010 (105)	2007 - 2008	Kenya	No
McCall, 2020 (60)	2017 - 2018	United States of America	No
O'Brien, 2017 (98)	2016 - 2016	Uganda	No
Prevost, 2015 (27)	2013 - 2014	France	Yes
Wong, 2013 (86)	2006 - 2007	United States of America	No
Zhou, 2014 (109)	2013 - 2013	China	No

Zhou, 2016 (110)	2014 - 2014	China	No
Bocaparvovirus			
McCall, 2020 (60)	2017 - 2018	United States of America	No
Cacipacore virus			
O'Brien, 2017 (98)	2016 - 2016	Uganda	No
Chikungunya			
McCall, 2020 (60)	2017 - 2018	United States of America	No
Circovirus			
O'Brien, 2017 (98)	2016 - 2016	Uganda	No
Coronavirus			
McCall, 2020 (60)	2017 - 2018	United States of America	No
Cosavirus			
Prevost, 2015 (27)	2013 - 2014	France	Yes
Cryptosporidium			
Heitman, 2002 (44)	1998 - 2000	Canada	No
Martins, 2019 (116)	2014 - 2015	Brazil	No
Deltaretrovirus			
McCall, 2020 (60)	2017 - 2018	United States of America	No
E. Coli			
Hutinel, 2019 (55)	2016 - 2016	Sweden	Yes
Yang, 2014 (120)	2010 - 2011	United States of America	No
Yao, 2017 (119)	2011 - 2013	Spain	No
Eastern equine encephalitis			
McCall, 2020 (60)	2017 - 2018	United States of America	No
Ebolavirus			
O'Brien, 2017 (98)	2016 - 2016	Uganda	No
Enterovirus (non-polio)			
Aw, 2010 (150)	2007 - 2007	Singapore	Yes
Antona, 2007 (32)	2000 - 2004	France	Yes
Berchenko, 2017 (39)	2013 - 2013	Isreal (and Palestine)	Yes

Bisseux, 2018 (61)	2014 - 2015	France	No
Bisseux, 2020 (51)	2014 - 2015	France	Yes
Cesari, 2010 (89)	2005 - 2008	Italy	No
Delogu, 2018 (68)	2009 - 2015	Italy	No
Farias, 2018 (91)	2013 - 2014	Argentina	No
Farias, 2019 (99)	2009 - 2014	Argentina	Yes
Grabow, 1999 (84)	1996 - 1997	South Africa	No
Harvala, 2014 (48)	2009 - 2010	United Kingdom (Scotland)	Yes
Ivanova, 2019 (36)	2004 - 2017	Russia	Yes
Kiulia, 2010 (105)	2007 - 2008	Kenya	No
Lizasoain, 2018 (85)	2011 - 2013	Uruguay	No
Lu, 2015 (43)	2009 - 2012	China	Yes
Majumdar, 2018 (88)	2015 - 2015	United Kingdom (Scotland)	No
McCall, 2020 (60)	2017 - 2018	United States of America	No
Monge, 2018 (31)	2007 - 2016	Netherlands	Yes
O'Brien, 2017 (98)	2016 - 2016	Uganda	No
Ozawa, 2019 (90)	2013 - 2016	Japan	No
Pavlov, 2006 (80)	2001 - 2003	South Africa	Yes
Pellegrinelli, 2013 (87)	2005 - 2010	Italy	No
Pellegrinelli, 2017 (74)	2012 - 2015	Italy	Yes
Pellegrinelli, 2019 (94)	2016 - 2016	Italy	No
Prevost, 2015 (27)	2013 - 2014	France	Yes
Tiwari, 2018 (47)	2007 - 2009	India	Yes
Wieczorek, 2015 (92)	2011 - 2011	Poland	No
Wong, 2013 (86)	2006 - 2007	United States of America	No
Zheng, 2013 (95)	2009 - 2012	China	No
Erythroparvovirus			
McCall, 2020 (60)	2017 - 2018	United States of America	No
Giardia			
Ajonina, 2013 (117)	N/A	Germany	No
Heitman, 2002 (44)	1998 - 2000	Canada	No

Majumdar, 2018 (93)	2013 - 2017	UK (Scotland and Englad); Pakistan; Senegal	No
Martins, 2019 (116)	2014 - 2015	Brazil	No
Gammaretrovirus			
McCall, 2020 (60)	2017 - 2018	United States of America	No
Hepatitis A			
Aw, 2010 (150)	2007 - 2007	Singapore	Yes
Béji-Hamza, 2014 (62)	2007 - 2008	Tunisia	Yes
Bisseux, 2018 (61)	2014 - 2015	France	No
Farkas, 2018 (96)	2016 - 2017	United Kingdom (Wales)	No
Hellmér, 2014 (30)	2013 - 2013	Sweden	Yes
Kiulia, 2010 (105)	2007 - 2008	Kenya	No
La Rosa, 2014 (33)	2012 - 2013	France	Yes
O'Brien, 2017 (98)	2016 - 2016	Uganda	No
Pellegrinelli, 2019 (94)	2016 - 2016	Italy	No
Prevost, 2015 (27)	2013 - 2014	France	Yes
Yanez, 2014 (28)	2009 - 2010	Argentina	Yes
Hepatitis C			
McCall, 2020 (60)	2017 - 2018	United States of America	No
Hepatitis E			
Alfonsi, 2018 (26)	2012 - 2016	Italy	Yes
Beyer, 2020 (45)	2014 - 2019	Germany	Yes
Bisseux, 2018 (61)	2014 - 2015	France	No
Farkas, 2018 (96)	2016 - 2017	United Kingdom (Wales)	No
Garcia, 2012 (100)	2010 - 2011	Brazil	No
Hellmér, 2014 (30)	2013 - 2013	Sweden	Yes
Iaconelli, 2020 (113)	2011 - 2019	Italy	No
McCall, 2020 (60)	2017 - 2018	United States of America	No
Prevost, 2015 (27)	2013 - 2014	France	Yes
Ram, 2016 (49)	2013 - 2015	Isreal	Yes

Wassaf, 2014 (29)	2007; 2009 - 2011	Argentina	Yes
Hepatovirus			
Garcia, 2012 (100)	2010 - 2011	Brazil	No
HIV			
McCall, 2020 (60)	2017 - 2018	United States of America	No
Human bocavirus			
Shaheen, 2020 (115)	2017 - 2018	Egypt	No
Human papillomavirus (HPV)			
McCall, 2020(60)	2017 - 2018	United States of America	No
O'Brien, 2017 (98)	2016 - 2016	Uganda	No
Lymphocryptovirus			
McCall, 2020 (60)	2017 - 2018	United States of America	No
Mastadenovirus			
Lun, 2019 (114)	2016 - 2017	Australia	Yes
Norovirus			
Aw, 2010 (150)	2007 - 2007	Singapore	Yes
Bisseux, 2018 (61)	2014 - 2015	France	No
Farkas, 2018 (96)	2016 - 2017	United Kingdom (Wales)	No
Fioretti, 2018 (57)	2013 - 2014	Brazil	Yes
Fumian et al 2019 (42)	2013 - 2014	Brazil	Yes
Garcia, 2012 (100)	2010 - 2011	Brazil	No
Grøndahl-Rosado, 2014 (97)	2011 - 2012	Norway	Yes
Hassine-Zaafrane, 2014 (50)	2007 - 2010	Tunisia	Yes
Hellmér, 2014 (30)	2013 - 2013	Sweden	Yes
Kazama, 2016 (58)	2012 - 2013	Japan	Yes
Kazama, 2017 (25)	2013 - 2016	Japan	Yes
Kiulia, 2010 (105)	2007 - 2008	Kenya	No
La Rosa, 2010 (106)	2007 - 2007	Italy	No
Mabasa, 2018 (107)	2015 - 2016	South Africa	No
McCall, 2020 (60)	2017 - 2018	United States of America	No

Prevost, 2015 (27)	2013 - 2014	France	Yes
Tao, 2015 (108)	2013 - 2013	China	No
Orthopoxvirus			
McCall, 2020 (60)	2017 - 2018	United States of America	No
Parechovirus			
Abe, 2016 (41)	2012 - 2014	Japan	Yes
Bisseux, 2018 (61)	2014 - 2015	France	No
Harvala, 2014 (48)	2009 - 2010	United Kingdom (Scotland)	Yes
Picobirnavirus			
O'Brien, 2017 (98)	2016 - 2016	Uganda	No
Poliovirus			
Antona, 2007 (32)	2000 - 2004	France	Yes
Berchenko, 2017 (39)	2013 - 2013	Isreal (and Palestine)	Yes
Cesari, 2010 (89)	2005 - 2008	Italy	No
Chowdhary, 2008 (73)	2004 - 2006	India	Yes
Coulliette-Salmond, 2019 (72)	2016 - 2017	Haiti	No
Cowger, 2017 (40)	2011 - 2013	Pakistan	Yes
Delogu, 2018 (68)	2009 - 2015	Italy	No
Deshpande, 2003 (76)	2001 - 2001	India	Yes
Esteves-Jaramillo, 2014 (63)	2010 - 2010	Mexico	Yes
Grabow, 1999 (84)	1996 - 1997	South Africa	No
González, 2019 (70)	2015 - 2015	Colombia	No
Hellmér, 2014 (30)	2013 - 2013	Sweden	Yes
Ivanova, 2019 (36)	2004 - 2017	Russia	Yes
Lodder, 2012 (59)	2011 - 2011	Netherlands	Yes
Manor, 1999 (37)	1989 - 1997	Israel (and Palestine)	Yes
Manor, 2007 (83)	1989 - 2005	Israel (and Palestine)	No
Manor, 2014 (77)	2013 - 2013	Israell	Yes
Más Lago, 2003 (65)	1997 - 1998	Cuba	Yes
Muluh, 2016 (75)	2012 - 2015	Nigeria	Yes
Nakamura, 2015 (64)	2010 - 2013	Japan	Yes
de Oliveira Pereira, 2016 (69)	2011 - 2012	Brazil	No
O'Reilly, 2018 (38)	2011 - 2015	Pakistan	Yes

Ozawa, 2019 (90)	2013 - 2016	Japan	No
Pavlov, 2006 (80)	2001 - 2003	South Africa	Yes
Pellegrinelli, 2013 (87)	2005 - 2010	Italy	No
Pellegrinelli, 2017 (74)	2012 - 2015	Italy	Yes
Richter, 2005 (71)	2005 - 2007	Cyprus	No
Shulman, 2006 (79)	1998 - 2006	Isreal (and Palestine)	No
Tao, 2010 (81)	2009 - 2009	China	Yes
Wahjuhono, 2014 (66)	2004 - 2007	Indonesia	No
Vinjé, 2004 (82)	2000 - 2000	Haiti; Dominican Republic	Yes
Yoshida, 2000 (78)	1993 - 2015	Japan	No
Polyomavirus			
Farkas, 2018 (96)	2016 - 2017	United Kingdom (Wales)	No
Garcia, 2012 (100)	2010 - 2011	Brazil	No
Torres, 2016 (111)	2005 - 2006; 2011 - 2013	Argentina	No
Roseolovirus			
McCall, 2020 (60)	2017 - 2018	United States of America	No
Rotavirus			
Barril, 2015 (104)	2009 - 2011	Argentina	No
Bisseux, 2018 (61)	2014 – 2015	France	No
Fumian, 2011 (67)	2009 - 2010	Brazil	No
Hassine-Zaafrane, 2015 (46)	2007 - 2010	Tunisia	Yes
Hellmér, 2014 (30)	2013 - 2013	Sweden	Yes
Kargar, 2013 (102)	2010 - 2011	Iran	No
Kiulia, 2010 (105)	2007 - 2008	Kenya	No
Kumazaki, 2015 (53)	2007 - 2012	Japan	Yes
Motayo, 2016 (101)	2014 - 2015	Nigeria	No
O'Brien, 2017 (98)	2016 - 2016	Uganda	No
Prevost, 2015 (27)	2013 - 2014	France	Yes
Ruggeri, 2015 (56)	2010 - 2011	Italy	Yes
Rubivirus (rubella)			
McCall, 2020 (60)	2017 - 2018	United States of America	No

Salivirus			
Prevost, 2015 (27)	2013 - 2014	France	Yes
Salmonella			
Diemert, 2019 (34)	2010 - 2011	United States of America	Yes
Li, 2011 (103)	2007 - 2008	China	No
Vincent, 2007 (35)	2003 - 2005	United States of America	Yes
Yan, 2018 (52)	2010 - 2011	United States of America	Yes
Sapovirus			
Farkas, 2018 (96)	2016 - 2017	United Kingdom (Wales)	No
Fioretti, 2016 (54)	2013 - 2014	Brazil	Yes
Garcia, 2012 (100)	2010 - 2011	Brazil	No
Kiulia, 2010 (105)	2007 - 2008	Kenya	No
McCall, 2020 (60)	2017 - 2018	United States of America	No
Scaffold virus			
Bonanno Ferraro, 2020 (112)	2017 - 2018	Italy	No
Simplexvirus			
McCall, 2020 (60)	2017 - 2018	United States of America	No
Tanapox virus			
O'Brien, 2017 (98)	2016 - 2016	Uganda	No
Torque teno virus			
O'Brien, 2017 (98)	2016 - 2016	Uganda	No
Varicellovirus (chickenpox)			
McCall, 2020 (60)	2017 - 2018	United States of America	No

[a] Web appendix 1 contains further information on each study including sampling site, the number of samples, the amount of wastewater sampled, the type of wastewater sample, and the laboratory method used.

Figure Legends

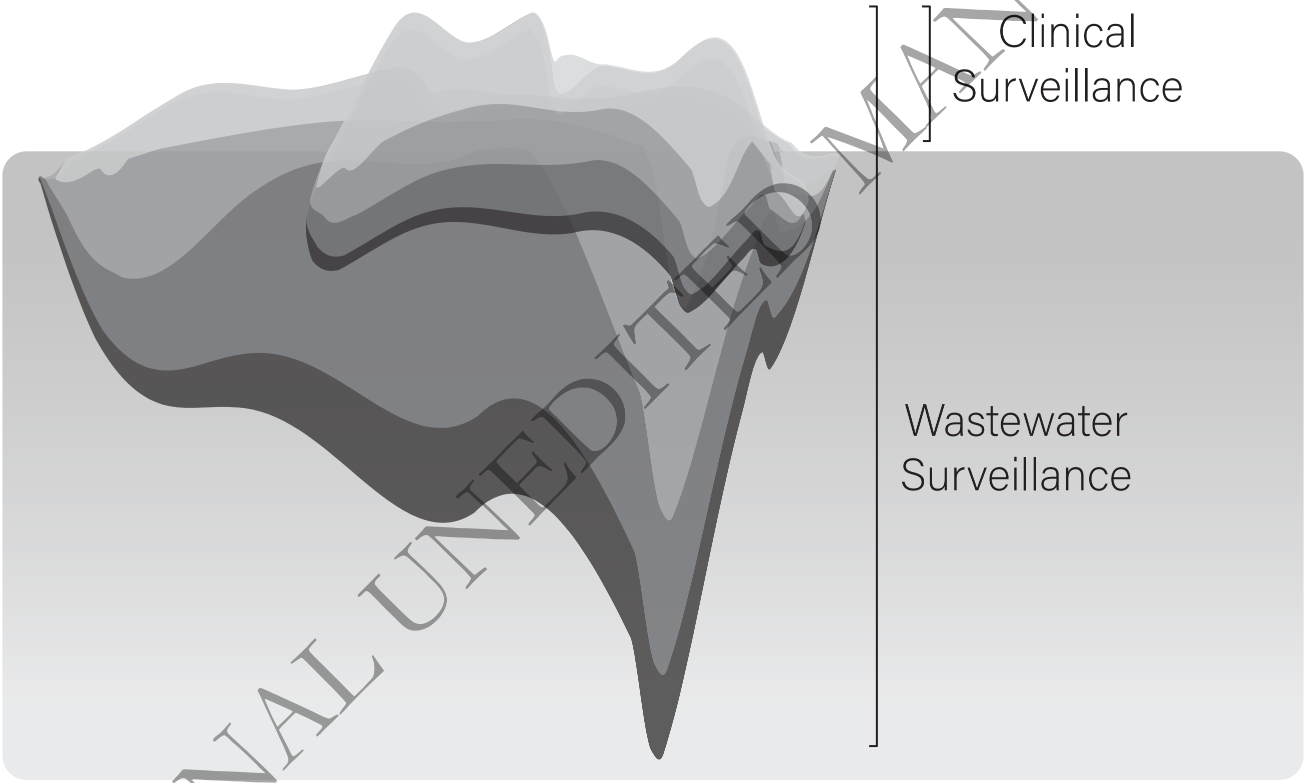
Figure 1. Infectious disease transmission in a population is often viewed as an iceberg. Only a fraction of infectious disease transmission is ever visible, as cases, hospitalizations, and deaths arise and are counted. Clinical surveillance captures this fraction of visible infectious disease transmission. Wastewater surveillance captures the visible as well as the "invisible" information on infectious disease transmission, including infections that do not result in cases, hospitalizations, or deaths. Infections may be "invisible" for a variety of reasons including: a lack of symptoms, individuals not seeking a diagnostic test or treatment, lack of access to a diagnostic test or treatment, or even clinical systems unable or unwilling to report cases.

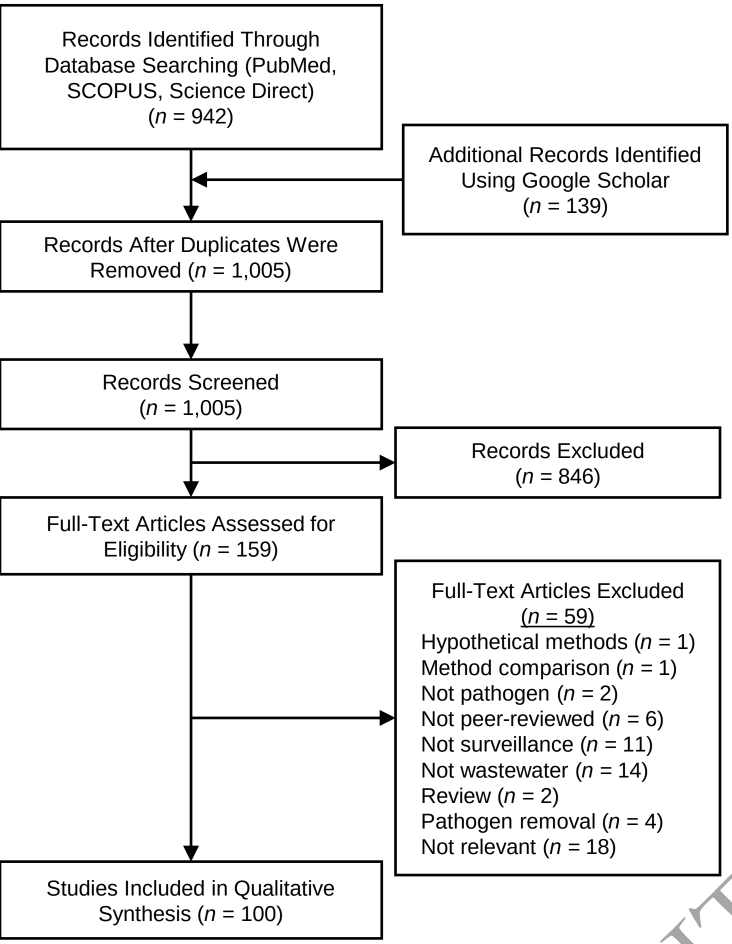
Figure 2. PRISMA flow chart of articles included in the review. Reasons for exclusion include: hypothetical Models – the experiment was hypothetical and no data were collected; methods comparison – the paper compared multiple recovery methods; not pathogen – paper focused on non-communicable diseases (e.g. diabetes); not surveillance – sampled only once or for non-surveillance purposes; not WW-based – wastewater was not directly tested; pathogen removal – paper looked at removal techniques of pathogens in wastewater; not relevant* - e.g. diseases not tied to human population, effect on other species/animals

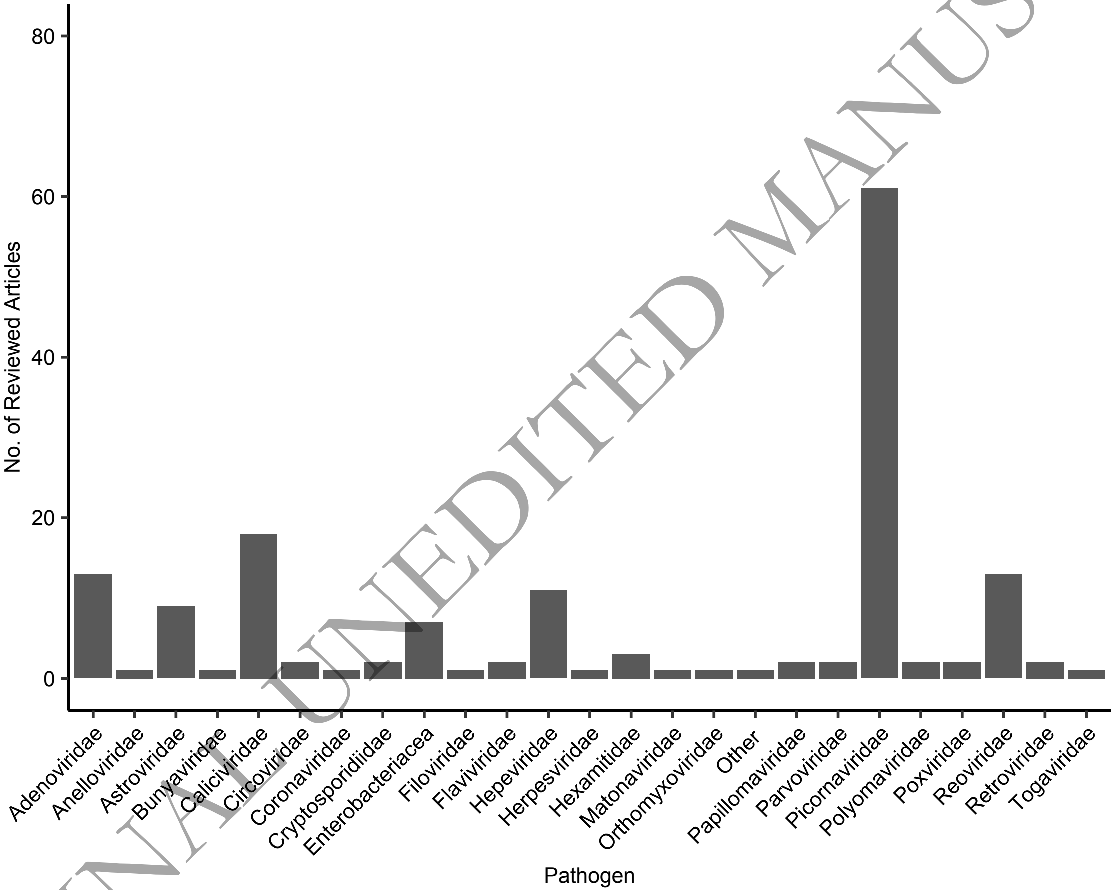
Figure 3. Frequency of the families of pathogens found in wastewater in the published literature.

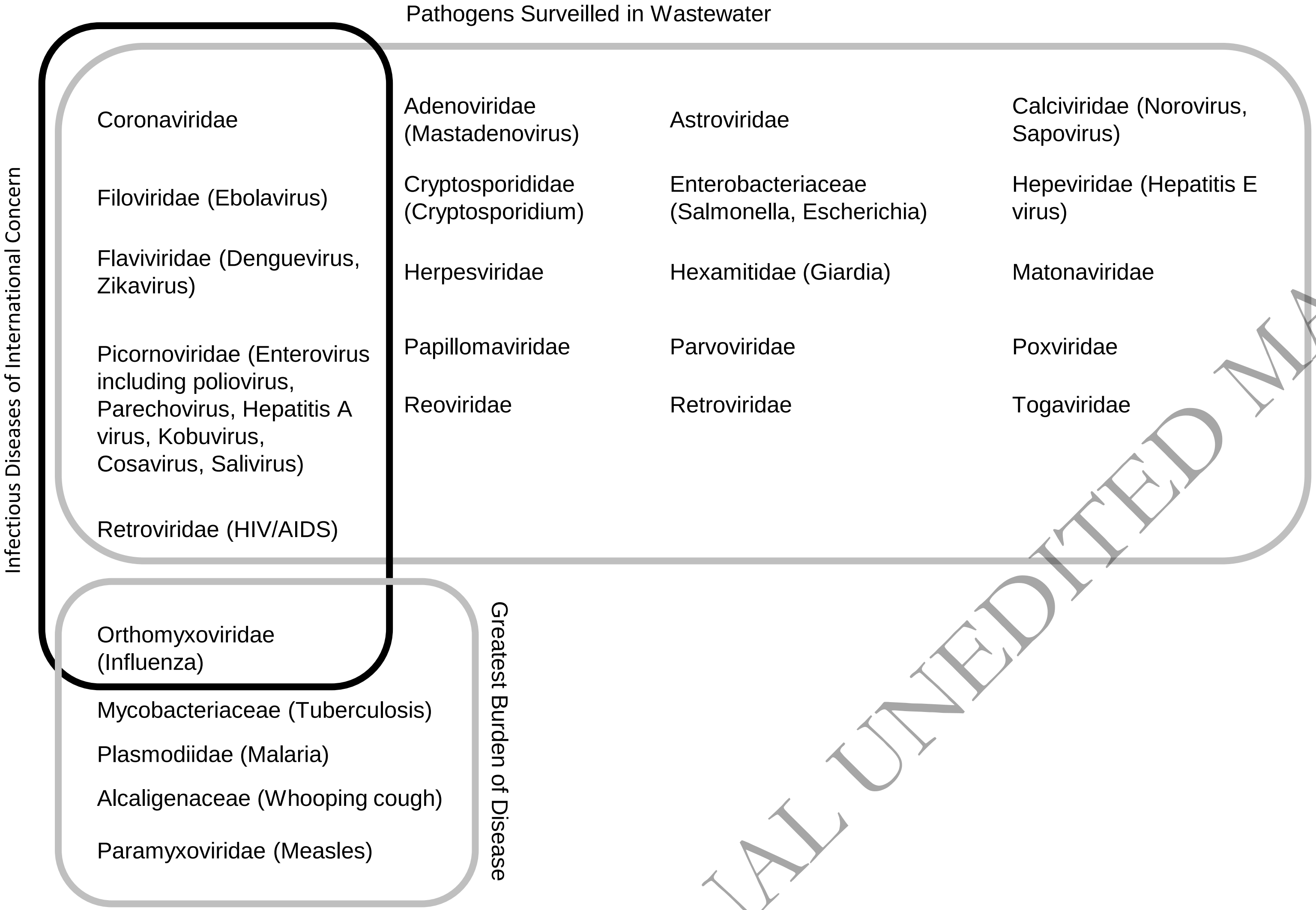
Figure 4. Pathogens historically surveilled in wastewater are not reflected in the greatest burden of disease except for diarrheal diseases. Many infectious diseases of international concern have been surveilled in wastewater. HIV/AIDS has been detected in wastewater (127), although no study fits our inclusion criteria. Influenza was not detected in wastewater during H1N1 pandemic (swine flu) (133), but many groups including ours are trying to adapt wastewater surveillance to various strains of influenza and there is report of success (132). Tuberculosis is a known risk to wastewater treatment plant operators (128), and so wastewater surveillance of tuberculosis is likely possible. Malaria can be readily diagnosed in human stool (131) suggesting that wastewater surveillance is likely possible.

Figure 5. Frequency of reviewed studies linking what was found in the wastewater to measures of infectious disease transmission, evaluation of a public health intervention, or the use of the wastewater surveillance to guide public health response or policy.


Clinical Surveillance
Wastewater Surveillance


Records Identified Through Database Searching (PubMed, SCOPUS, Science Direct) (*n* = 942)
Additional Records Identified Using Google Scholar (*n* = 139)
Records After Duplicates Were Removed (*n* = 1,005)
Records Screened (*n* = 1,005)
Records Excluded (*n* = 846)
Full-Text Articles Assessed for Eligibility (*n* = 159)
Full-Text Articles Excluded (*n* = 59)
Hypothetical methods (*n* = 1)
Method comparison (*n* = 1)
Not pathogen (*n* = 2)
Not peer-reviewed (*n* = 6)
Not surveillance (*n* = 11)
Not wastewater (*n* = 14)
Review (*n* = 2)
Pathogen removal (*n* = 4)
Not relevant (*n* = 18)
Studies Included in Qualitative Synthesis (*n* = 100)


80
60
40
20
0
No. of Reviewed Articles
Adenoviridae
Anelloviridae
Astroviridae
Bunyaviridae
Caliciviridae
Circoviridae
Coronaviridae
Cryptosporidiidae
Enterobacteriacea
Filoviridae
Flaviviridae
Hepeviridae
Herpesviridae
Hexamitidae
Matonaviridae
Orthomyxoviridae
Other
Papillomaviridae
Parvoviridae
Picornaviridae
Polyomaviridae
Poxviridae
Reoviridae
Retroviridae
Togaviridae
Pathogen



Pathogens Surveilled in Wastewater

Infectious Diseases of International Concern

Greatest Burden of Disease

Coronaviridae

Filoviridae (Ebolavirus)

Flaviviridae (Denguevirus, Zikavirus)

Picornoviridae (Enterovirus including poliovirus, Parechovirus, Hepatitis A virus, Kobuvirus, Cosavirus, Salivirus)

Retroviridae (HIV/AIDS)

Adenoviridae (Mastadenovirus)

Astroviridae

Calciviridae (Norovirus, Sapovirus)

Cryptosporididae (Cryptosporidium)

Enterobacteriaceae (Salmonella, Escherichia)

Hepeviridae (Hepatitis E virus)

Herpesviridae

Hexamitidae (Giardia)

Matonaviridae

Papillomaviridae

Parvoviridae

Poxviridae

Reoviridae

Retroviridae

Togaviridae

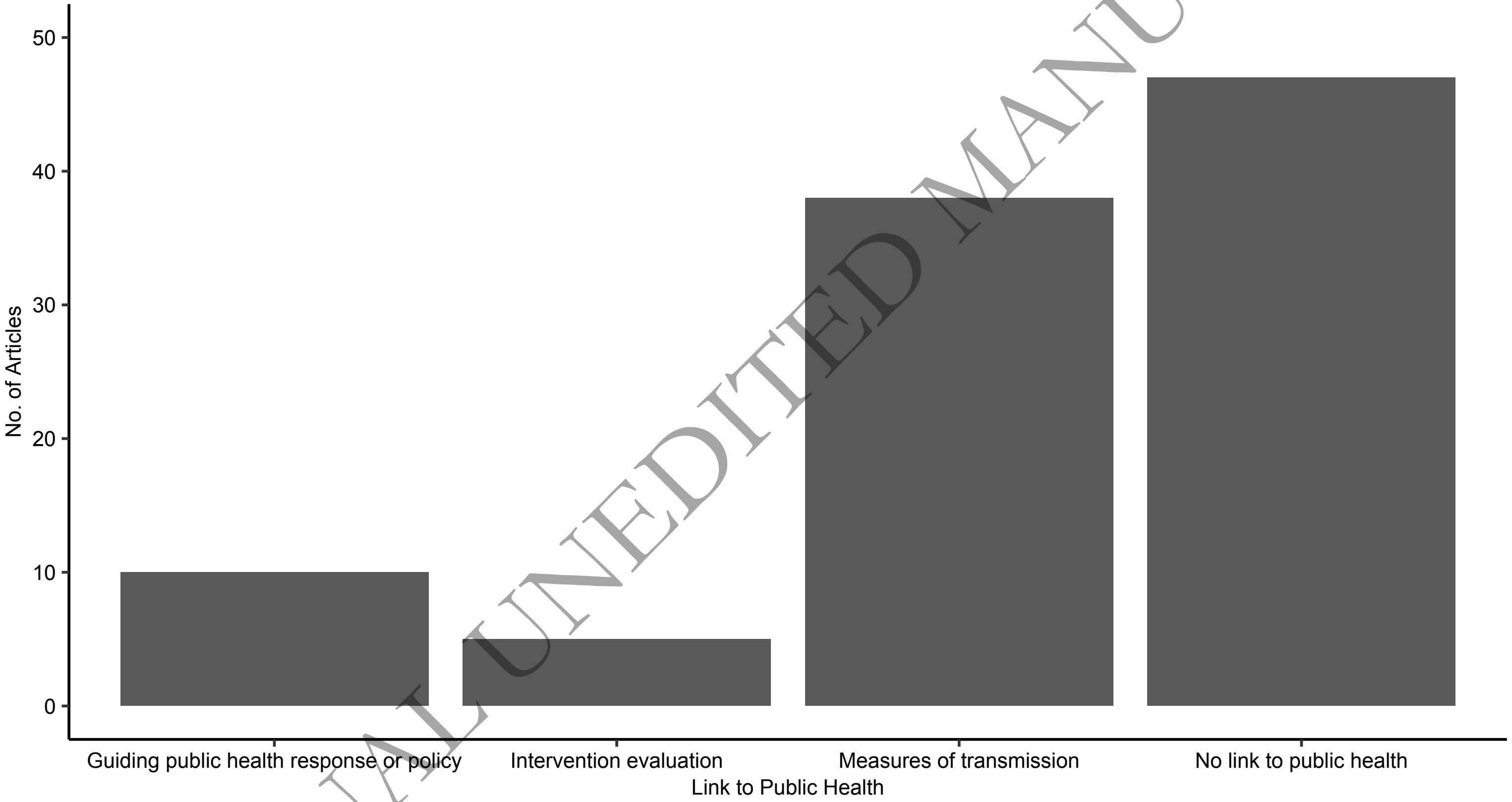
Orthomyxoviridae (Influenza)

Mycobacteriaceae (Tuberculosis)

Plasmodiidae (Malaria)

Alcaligenaceae (Whooping cough)

Paramyxoviridae (Measles)


50
40
30
20
10
0
No. of Articles
Guiding public health response or policy
Intervention evaluation
Measures of transmission
No link to public health
Link to Public Health