



Norovirus detection in wastewater and its correlation with human gastroenteritis: a systematic review and meta-analysis

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Abstract

Norovirus (NoV) is a major cause of sporadic cases and outbreaks of acute gastroenteritis (AGE), thereby imposing threat to health globally. It is unclear how quantitation of wastewater NoV reflects the incidence of human AGE infections; therefore, we conducted this systematic review and meta-analysis of published NoV wastewater surveillance studies. A literature search was performed, and all studies on NoV wastewater surveillance were identified. Quantitative results were evaluated. The results showed that the overall detection rate of NoV in wastewater was 82.10% (95% confidence interval [CI]: 74.22–89.92%); NoV concentration was statistically significant in terms of season ($P < 0.001$), with higher concentration in spring and winter. There were positive correlations between NoV GII concentration in wastewater and GII AGE cases ($r_s = 0.51$, 95% CI: 0.18–0.74, $I^2 = 0\%$), total AGE cases ($r_s = 0.40$, 95% CI: 0.15–0.61, $I^2 = 23\%$) and NoV outbreaks ($r_s = 0.47$, 95% CI: 0.30–0.62, $I^2 = 0\%$). Results of cross-correlation analysis of partial data indicated that variations in GII concentration were consistent with or ahead of those in the number of AGE cases. The diversity of NoV genotypes in wastewater was elucidated, and the dominant strains in wastewater showed a consistent temporal distribution with those responsible for human AGE. Our study demonstrated the potential association of NoV detected in wastewater with AGE infections, and further studies are needed to confirm this conclusion.

Keywords Wastewater surveillance · Norovirus · Human gastroenteritis · Detection · Meta-analysis · Systematic review

Introduction

Norovirus (NoV) is the leading cause of sporadic cases and outbreaks of acute gastroenteritis (AGE) in all age groups, causing more than 699 million infections and approximately 212,000 deaths worldwide each year (Lopman et al. 2016; Netzler et al. 2019). NoVs are non-enveloped viruses of the Caliciviridae family that have a single-stranded RNA genome of approximately 7.5 kb in length which contain

three open reading frames (ORFs): ORF1 encodes a poly-protein, ORF2 encodes the major structural protein (VP1), and ORF3 encodes the minor structural protein (VP2). Based on the complete capsid amino acid sequences, NoVs were divided into 10 genogroups (GI–GX) and a further subdivision into 49 genotypes (Chhabra et al. 2019). GI, GII, and GIV are reported to infect humans. Due to the genetic diversity and evolutionary complexity, there were at least six NoV mutant strains known to cause worldwide pandemics in the last 20 years (Nordgren and Svensson 2019).

Continuous monitoring for NoV is imperative. Several inter-regional NoV surveillance networks, including NoroNet (<https://www.rivm.nl/en/noronet>) and CaliciNet (<https://www.cdc.gov/norovirus/reporting/calicinet/>), have been developed worldwide. NoroNet collects molecular epidemiological data on NoV infections from 19 countries in Europe, Asia, and Australia (Green 2018); whereas, CaliciNet monitors NoV outbreaks mainly in the USA as well as in parts of China (Cannon et al. 2017; Jin et al. 2020). Clinical surveillance relies primarily on clinical samples from patients

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at healthcare facilities, which can barely focus on people with mild infections and asymptomatic infections. Evidence favors the notion that NoV may cause higher rates of asymptomatic acute gastroenteritis infections within household and community (de Wit et al. 2001; Quee et al. 2020; Teunis et al. 2015).

Wastewater surveillance/wastewater-based epidemiology (WBE) is another ideal approach for monitoring viruses prevalence and to date has been applied to screen for a wide range of water-borne and non-water-borne viruses (O'Brien and Xagorarakis 2019). It bridges the gap of individual clinical testing by providing an unbiased estimate of disease prevalence in the whole population. Poliovirus wastewater surveillance as a complementary method to the Global Polio Eradication Initiative has been included in the World Health Organization (WHO) guidelines for environmental poliovirus surveillance (Sein 2013). During the COVID-19 pandemic, detection technology and method for wastewater surveillance were conducted globally as SARS-CoV-2 screening approach within communities. Besides early warnings for localized outbreaks (Chavarria-Miró et al. 2021; Medema et al. 2020), several studies further found the consistent trends in the temporal distribution of SARS-CoV-2 concentration in raw sewage and local cases (Daughton 2020; Peccia et al. 2020; Weidhaas et al. 2021; Wurtzer et al. 2020).

Host-specific NoV sheds through the feces of infected individuals—including those with severe, mild, and asymptomatic infections—and enters wastewater, following which it can remain at high concentration in the water (Ngazoa et al. 2008). NoV cannot replicate in nonhost organisms in the environmental media, which means that the measured NoV concentration of raw wastewater can reflect AGE infection in the local population, theoretically. However, standard protocols and procedures for NoV detection have not yet been established in the field of viral wastewater surveillance, and it is unclear how NoV detection in wastewater quantitatively reflects the incidence of human AGE infections. On the basis of the above evidence, we performed a systematic review and meta-analysis of past NoV wastewater surveillance studies to explore and estimate the correlation between NoV occurrence in wastewater and AGE in the population.

Materials and methods

Search strategy

A literature search was conducted in PubMed and Embase databases from inception to August 13, 2021. The search keywords were as follows: (“sewage” OR “wastewater”) AND (“norovirus” OR “Norwalk-like virus” OR “small round structured viruses”). Hand searching and screening

of the reference list was also conducted. The literature was screened by reading the title, and after eliminating irrelevant literature, study eligibility was further assessed by reading the abstract and full text. Screening abstracts, articles that meet the following criteria are included first:

- (a) reported outcome indicators reflecting virus detection in wastewater, such as NoV detection rate, viral RNA concentration, and temporal distribution by genotype;
- (b) continuous sampling for at least 3 months.

Then reading the full text, the final selection of eligible articles was based on the following exclusion criteria:

- (a) studies that did not classify NoV genogroups;
- (b) case reports or case series of viral gastroenteritis outbreaks;
- (c) studies that did not report detailed data;
- (d) wastewater type was not raw wastewater (raw wastewater was defined as influent sewage before or after primary screening and settling from the municipal wastewater treatment plant);
- (e) full text not available; or
- (f) reported duplicate data.

The literature was screened, selected, and cross-checked by two researchers independently. Disagreements, if any, were resolved through discussion or consultation with a third researcher.

Data extraction and assessment

Data for the following variables were extracted from all eligible articles: (a) basic information: title of study, first author, year of publication, and country or region; (b) sampling and processing information: sample size, collection season or month, virus concentration method, and polymerase chain reaction (PCR) assay; (c) primary outcome indicators: NoV detection rate, viral concentration, and genotyping information for wastewater detection; (d) other outcome indicators, if available: content reflecting population prevalence, i.e., number of GI or GII AGE cases, number of NoV outbreak, or number of total AGE cases; the limit of detection (LOD). GetData Graph Digitizer, version 2.25, was used to extract the required data from the images.

Each included study was independently reviewed and assessed by two researchers according to the AHRQ cross-sectional study assessment scale. We modified some of the items to accommodate the included articles (Supplementary Sect. 1).

Statistical analysis

During data processing, missing data on concentration that were below LOD were replaced with a value equal to the peer-reviewed LOD divided by square root of 2. The units of NoV RNA concentration were unified as log10 genome copies per liter (lg GC/L), to make the data close to the normal distribution.

IBM SPSS Statistics 25.0 and R 4.0.3 software programs were used for data analyses in this study. NoV detection rate was subjected to Freeman-Tukey double arcsine transformation. One-way analysis of variation (ANOVA) was used to assess the statistical significance of NoV concentration. In addition, Spearman’s correlation coefficients in each study that provided raw data was calculated. To estimate the standard errors, coefficients were converted to Fisher’s Z values. Meta-analysis and meta-regression were performed using the meta package in R. Heterogeneity among studies was determined using the Q test statistic and I^2 . For $P < 0.05$ or $I^2 > 50%$, heterogeneity was considered to exist and a random-effects model was used; otherwise, a fixed-effects model was used.

Results

Search results

A total of 8688 studies were identified following the database search. After removing duplicates, 5719 studies remained for screening. By screening the title and abstract and after excluding irrelevant studies, 164 needed to be screened by reading the full text. Finally, 46 were selected for the analysis (Fig. 1).

Study characteristics and quality assessment

The characteristics and basic information of 46 included studies are presented in Table 1. According to WHO mortality stratum (World Health Organization 2003a, b), there were 29 studies from developed countries, 13 from low-mortality developing countries, and 4 from high-mortality developing countries. Most studies ($n = 28$) were sampled for ≤ 1 year, and only 4 studies were sampled for more than three years. Different methods were used for assessing the virus concentration, including adsorption-elution ($n = 16$),

Fig. 1 Flow diagram of included studies and the selection process

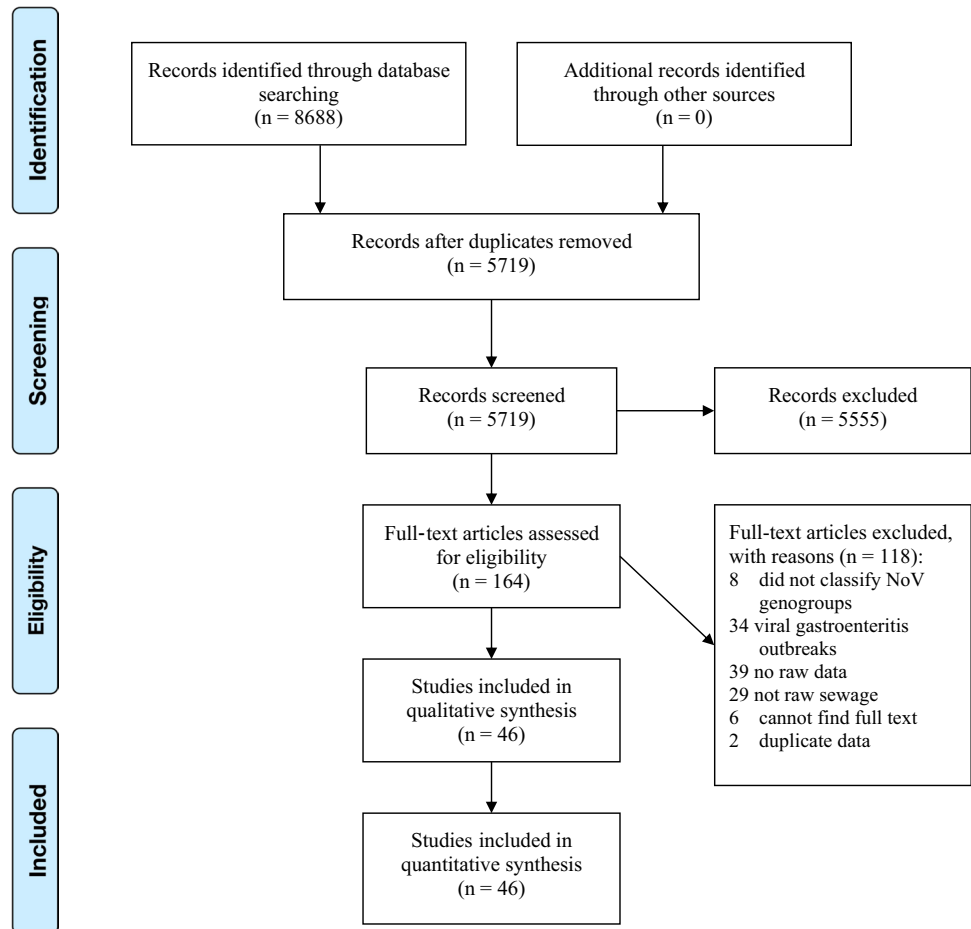


Table 1 Characteristics of included studies

Author	Country/region	Sampling time	Virus concentration method ^a	PCR	N	GI detection rate	GI detection rate	GIV detection rate	Outcome ^b	Genogroup	Reported seasonality	LOD (lg GC/L)
(Wang et al. 2020)	Sweden	2016.12–2017.12	4	qRT-PCR	26	1	1	0.73	②②	GI, GII, GIV	Yes	
(La Rosa et al. 2008)	Italy	2007.1–2007.12	5	RT-PCR	75			0.1	②③	GIV	No	
(Kazama et al. 2016)	Japan	2012.11–2013.3	2	qRT-PCR	17	0.82	0.65		①②③	GI, GII	Yes	
(Kamel et al. 2010)	Egypt	2006.4–2007.2	1	qRT-PCR	72	0.15	0.3		②③	GI, GII	No	
(Fioretti et al. 2018)	Brazil	2013.5–2014.5	4	qRT-PCR	52			0.52	②③	GIV	No	
(Carducci et al. 2006)	Italy	2004.5–2005.3	3	qRT-PCR	12	0.8	0.8		②②	GI, GII	Yes	
(Zhou et al. 2016)	China	2014.1–2014.12	1	qRT-PCR	23	1	1		③③	GI, GII	Yes	
(Victoria et al. 2016)	Uruguay	2011.3–2013.4	5	RT-PCR	116	0.31	0.65		③	GI, GII	Yes	
(Victoria et al. 2010)	Brazil	2005.1–2005.12	1	qRT-PCR	24	0.4	0.67		②②	GI, GII	No	
(Teixeira et al. 2016)	Brazil	2008.11–2010.10	1	RT-PCR	24			0.17	③	GIV	No	
(Teixeira et al. 2017)	Brazil	2008.11–2010.10	1	RT-PCR	24	0.79	0.71		③	GI, GII	No	
(Tao et al. 2015)	China	2013.1–2013.12	1	RT-PCR	24	1	1		③	GI, GII	No	
(Suffredini et al. 2018)	Italy	2011.1–2016.12	6	RT-PCR	19	0.84	0.84		③	GII	No	
(Skraber et al. 2011)	Luxembourg	2008–2009 winters	5	RT-PCR	78	0.44	0.97		③	GI, GII	No	
(Prado et al. 2011)	Brazil	2005–2008	1	qRT-PCR	12		0.25		②③	GII	No	
(Prado et al. 2019)	Brazil	2015.4–2016.3	3	qRT-PCR	48	0.94	0.98		②	GI, GII	No	
(Muscillo et al. 2013)	Italy	2011.5–2012.5	6	qRT-PCR	307			0.22	②③	GIV	No	
(Montazeri et al. 2015)	United States	2013.7–2014.6	5	qRT-PCR	12	0.83	0.83		②③	GI, GII	Yes	
(Masago et al. 2016)	Japan	2012.8–2013.12	2	qRT-PCR	70	0.71	0.81		②③	GI, GII	No	
(Mabasa et al. 2018)	South Africa	2015.4–2016.3	2	qRT-PCR	108	0.41	0.68		②③	GI, GII	Yes	
(La Rosa et al. 2010)	Italy	2007.5–2007.9	5	RT-PCR	64	0.94	0.92		③	GI, GII, GIV	No	
(Kitajima et al. 2012)	Japan	2005.3–2006.2	1	qRT-PCR	12	1	1		②③	GI, GII	Yes	
(Kazama et al. 2017)	Japan	2013–2016	2	qRT-PCR	156	0.58	0.79		①②③	GI, GII	Yes	GI = 4.5 GII = 4.6
(Hassine-Zaafraane et al. 2014)	Tunisia	2007.4–2010.4	5	RT-PCR	309	0.31	0.1		②③	GI, GII	No	
(Haramoto et al. 2011)	Japan	2003.7–2004.6	1	qRT-PCR	12	1	1		①	GI, GII	Yes	
(Han et al. 2014)	South Korea	2010.12–2012.5	1	RT-PCR	14		0.36	0.21	③	GI, GIV	No	
(Fumian et al. 2019)	Brazil	2013.4–2014.5	4	qRT-PCR	52	0.38	0.96		①②③	GI, GII	Yes	GI GII = 3.9
(Kobayashi et al. 2017)	Japan	2014.4–2015.3	2	qRT-PCR	25	1	0.4		①	GI, GII	Yes	
(Gurung et al. 2017)	Finland	2016.1–2016.4	1	qRT-PCR	14	0.71	1		①	GI, GII	Yes	GI GII = 3.90
(Amarasiri et al. 2018)	Japan	2013.10–2015.2	2	qRT-PCR	5		1		③	GII	No	
(Campos et al. 2016)	England	2009.6–2011.5	5	RT-PCR	41	0.83	1		②②	GI, GII	Yes	
(Pérez-Sautu et al. 2012)	Spain	2007.11–2009.4	2	qRT-PCR	54	1	1		②③	GI, GII	Yes	GI GII = 3.55

Table 1 (continued)

(Sima et al. 2011)	France	2009.10–2010.6	3	qRT-PCR	31	0.9	0.84	①	GI, GII	Yes	GI GII = 2.26
(Miura et al. 2015)	Japan	2010.12–2012.3	2	qRT-PCR	16		0.94	①	GII	Yes	GII = 1.25
(Masclaux et al. 2013)	Switzerland	2010–2011 summer&winter	2	qRT-PCR	62		0.97	①	GII	Yes	GII = 4.27
(Kauppinen et al. 2014)	Finland	2010.10–2011.10	1	qRT-PCR	19	0.95	1	①	GI, GII	Yes	
(Hellmér et al. 2014)	Sweden	2013.1–2013.5	4	qRT-PCR	7	0.71	0.86	②②	GI, GII	Yes	GI = 1.0
(Grøndahl-Rosado et al. 2014)	Norway	2011.1–2012.5	2	qRT-PCR	17	0.41	0.53	②②	GI, GII	Yes	GI = 3.60 GII = 4.04
(Da Silva et al. 2007)	France	2005.12–2006.12	6	qRT-PCR	81	0.98	1	①	GI, GII	Yes	GI = 3.45 GII = 2.36
(Aw and Gin 2010)	Singapore	2007.1–2007.6	2	qRT-PCR	18	1	1	③	GI, GII	No	
(Lu et al. 2021)	China	2013.1–2018.12	1	qRT-PCR	72	0.92	1	②③	GI, GII	Yes	GI GII = 5.0
(McCall et al. 2020)	United States	2017.11–2018.2	1	qRT-PCR	18		0.67	②②	GII	No	
(Lin et al. 2021)	China	2014–2016	1	RT-PCR	36	1	1	③	GI, GII	No	
(Santiso-Bellón et al. 2020)	Spain	2016.9–2017.9	5	qRT-PCR	46	0.7	0.76	③	GI, GII	No	
(Ibrahim et al. 2020)	Tunisia	2018.6–2019.4	1	qRT-PCR	20	0.85	1	①	GI, GII	Yes	
(Lun et al. 2018)	Australia	2014.7–2016.12	5	RT-PCR	12	1	1	②③	GI, GII	No	

^a1 Adsorption-extraction; 2 Polyethylene glycol precipitation; 3 Ultrafiltration; 4 Elution and skimmed-milk flocculation procedure; 5 Ultracentrifugation; 6 Other methods

^b① Concentration of NoV in wastewater; ② Information reflecting population prevalence; ③ Information of genotyping

polyethylene glycol precipitation ($n=11$), ultracentrifugation ($n=9$), elution and skimmed-milk flocculation procedure ($n=4$), ultrafiltration ($n=3$), and others ($n=3$). GII was the most frequently detected genogroup ($n=42$), with only few detected for GIV ($n=7$). Eighteen studies collected both wastewater samples and population gastrointestinal infection data, but only a part of them provided detailed data for calculating correlation coefficients, and the remainder described phylogenetic results for positive samples.

On assessing the quality of each study, seven articles were evaluated as having high quality, 32 as moderate, and seven as low, with an average quality score of 6.30 ± 1.93 (Supplementary Table S1). Regarding the assessment and adjustment of inhibition and recovery rates, approximately two-thirds of the studies did not report these rates.

Meta-regression of NoV detection rates

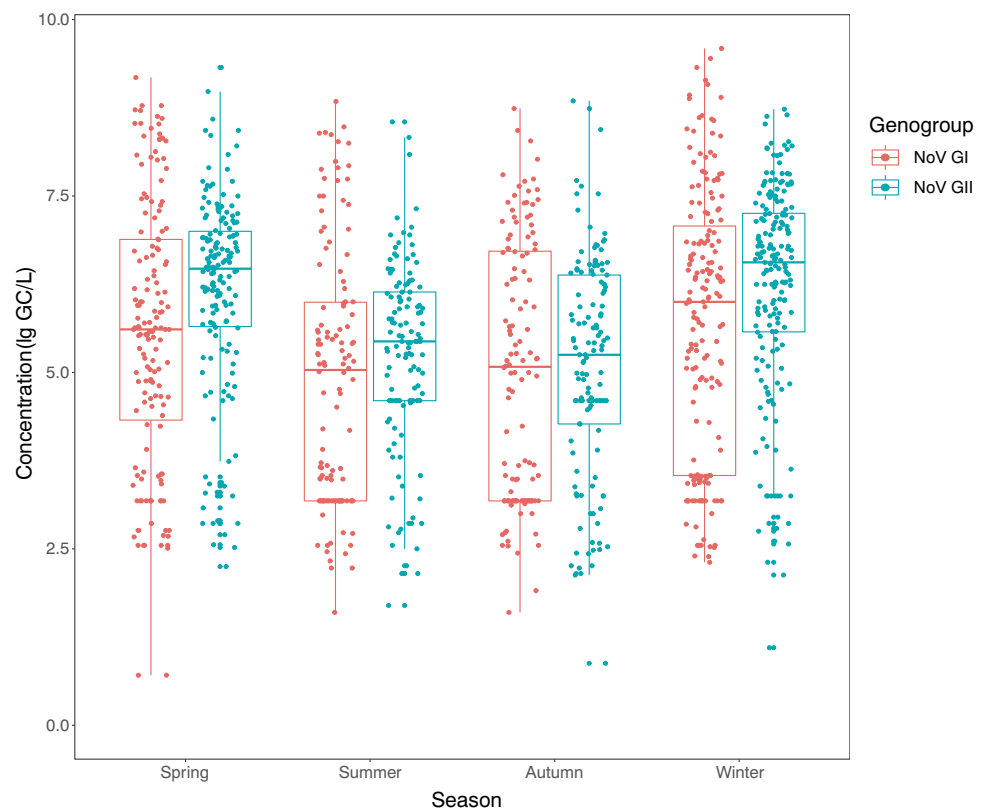
A meta-analysis was performed on the NoV detection rate reported in 46 studies, and the overall detection rate was 82.10% (95% confidence interval [CI]: 74.22–89.92%) (Supplementary Table S2). NoV genogroup, country mortality, PCR method, sampling duration, and virus concentration quantification method were used as variables for the univariate meta-regression analysis of NoV detection rates (Supplementary Table S3). The results showed that NoV genogroup and country mortality significantly affected the

heterogeneity of the meta-analysis results. When including both NoV genogroup and country mortality into the multi-factor regression model, the R^2 was 52.81%, which suggests that NoV genogroup and country mortality can explain part of the heterogeneity in detection rates. Greater detection rates in NoV GI (81.90%, 95% CI: 71.26–90.70%) and GII (88.04%, 95% CI: 77.23–96.05%) and countries with higher development levels and lower overall mortality (developed countries (87.33%, 95% CI: 79.22–93.87%), low-mortality developing countries (78.01%, 95% CI: 63.77–89.68%)) were observed compared to GIV (30.89%, 95% CI: 15.45–48.73%) and high-mortality developing countries (47.08%, 95% CI: 27.85–66.75%).

Seasonal differences in NoV concentration

Twenty-six studies reported data for NoV concentration in wastewater in different seasons, 22 studies monitored GI and GII, and four studies monitored only GII. NoV GIV was not included in the quantitative analysis owing to insufficient data. In total, the GI concentration in wastewater was 5.34 (95% CI: 5.18–5.49) lg GC/L and the GII concentration was 5.74 (95% CI: 5.62–5.87) lg GC/L. ANOVA results showed that the concentrations of GI and GII were statistically significant in terms of season ($P < 0.001$), with higher concentration observed in spring and winter than in summer and autumn (Fig. 2, Supplementary Table S4).

Fig. 2 Boxplot of seasonal variation of NoV GI and GII concentrations in wastewater



Correlation between NoV detection and population infection

Seven articles provided detailed monthly data on NoV concentration in wastewater and gastrointestinal infections in local populations. They were divided into different indicators (GI and GII AGE cases, total AGE cases, and NoV outbreaks) and analyzed separately. The percentage of NoV GI infection cases in AGE ranged from 0.00 to 8.00%, and the percentage of GII infection cases ranged from 12.00 to 64.34%. The number of AGE cases and NoV outbreaks varied widely depending on the size of the study area, but both indicators peaked during the cold season (November to May) (Supplementary Table S5).

Spearman's correlation coefficient was calculated based on raw data from seven studies, and the portion of GII in Carducci et al. (2006) study was not included in the calculations due to severe data deficiencies. The results of the correlation meta-analysis are shown in Fig. 3a, c, and e. Overall, significant positive correlations between the NoV GII concentration in wastewater and GII AGE cases ($r_s = 0.51$, 95% CI: 0.18–0.74, $I^2 = 0\%$), total AGE cases ($r_s = 0.40$, 95% CI: 0.15–0.61, $I^2 = 23\%$), and NoV outbreaks ($r_s = 0.47$, 95% CI: 0.30–0.62, $I^2 = 0\%$) were founded, while there was no correlation for NoV GI concentration and any of the above indicators. For GII, 32/86/97 data points were available for analysis from six studies. As shown in Fig. 3b, d, and f, these studies did not show consistent statistical significance, but the overall trends were similar and they were also considerably homogeneous: they were conducted in developed regions of Europe and Asia, sampled at relatively similar periods and were all graded as medium to high quality. The homogeneity was also indicated by the fact that I^2 statistics for heterogeneity tests were all below 25%, i.e., the inferred combined correlation coefficients were reasonable.

Notably, Kazama et al. (2017) conducted a cross-correlation analysis of the concentrations of GI and GII in weekly samples and the number of locally AGE cases. They reported that a significant correlation for GII was observed with a lag of -2 to $+6$ weeks, and the peak coefficient ($r = 0.51$) was observed at a time lag of 0 weeks. This indicated that changes in GII concentration in wastewater and the increase in the number of reported AGE cases occurred simultaneously. Therefore, the same analysis for other studies that sampled at a frequency of ≤ 2 weeks was performed. Similarly, peak coefficient time lags of zero, plus, or minus, indicated that the variation in virus concentration coincides with, lags, or exceeds the variation in the number of AGE cases (Kazama et al. 2017). It was observed only in the data of Wang et al. (2020) (sampling per 2 weeks): the concentration of GII in wastewater correlated with the number of total AGE cases at time lags of -6 to $+4$ weeks, with the peak occurring at a time lag of -2 weeks ($r = 0.61$). No

significant correlations were observed in the other eligible studies.

Temporal distribution of the NoV genotype

Thirty studies analyzed the genotypes of NoV in wastewater during 2005–2018. Figure 4 shows the prevalence dynamics of the different genotypes at the period with a high sampling frequency (winter 2012 to summer 2017), darker-color blocks represent higher detection rate. There were up to 17 genotypes of NoV with high detection rates and frequency in wastewater. In comparison with the NoV genotype distribution in human AGE infections, a similar trend was observed in wastewater, especially for GII (Supplementary Fig. S1).

For NoV, GI, GI.2, GI.5, and GI.3 were frequently detected in wastewater, and since the summer of 2014, GI.6 was continuously detected at a high and positive rate. For NoV, GII, GII.4, GII.17, GII.2, GII.3, and GII.13 were detected frequently and continuously; particularly, GII.4 was detected at a higher rate before 2015. A notable difference after 2015 was that GI.1, GI.5, GII.4, and GII.6 were no longer detected continuously, but GII.2 was detected more frequently.

Discussion

WBE has great potential in the field of infectious disease surveillance, where it can serve as one of routine passive screening tools applied in community units to reveal asymptomatic or preclinical states of disease. In response to the COVID-19 pandemic, more precise virus detection and molecular quantification methods were developed and updated by various wastewater monitoring laboratories. Undeniably, undefined methodological criteria are one of the current barriers to interpreting wastewater data when associating virus concentrations in wastewater with disease incidence in contributing populations quantitatively (Greenwald et al. 2021). This systematic review and meta-analysis comprehensively assessed NoV wastewater surveillance studies and quantitatively estimated the correlation between the occurrence of NoV in wastewater and AGE in the population.

In terms of the quality assessment of including studies, the overall quality of NoV wastewater surveillance studies was not high. And most of them did not consider (or did not state) the recovery rate of the virus and the possible inhibition effect, which may have led to the underestimation of the results. The short sampling period is another feature. Many studies chose one year as the sampling period because this allowed observation of the complete trend of changes in the NoV detection level in different seasons. However, long-term sampling could, in addition, provide a clearer

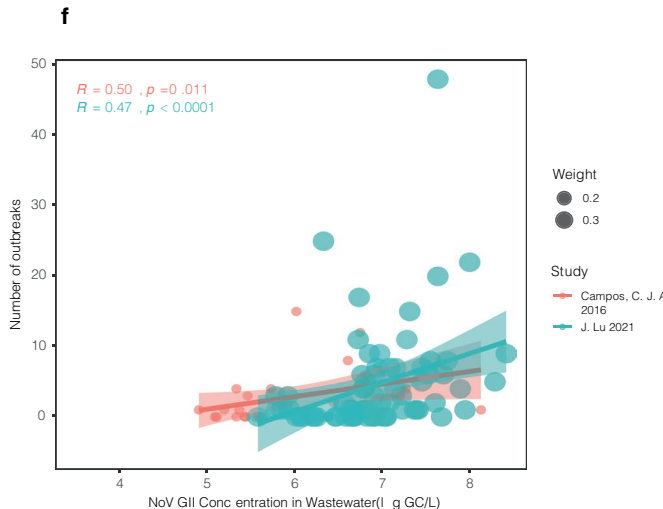
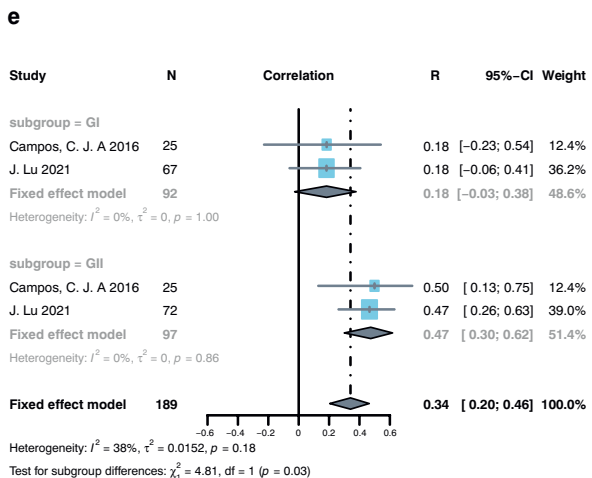
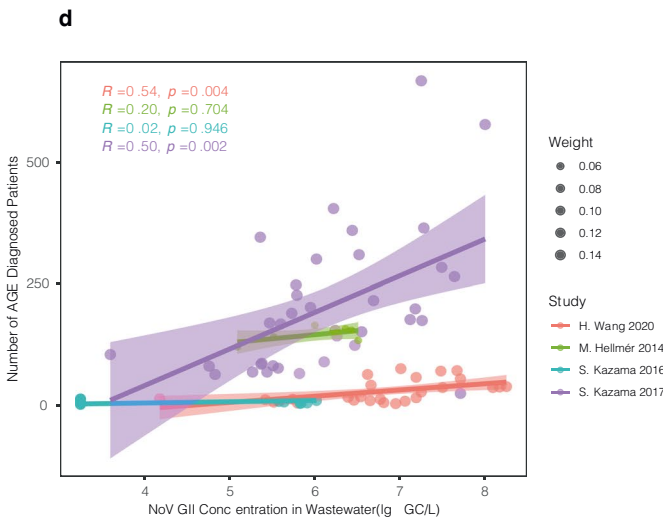
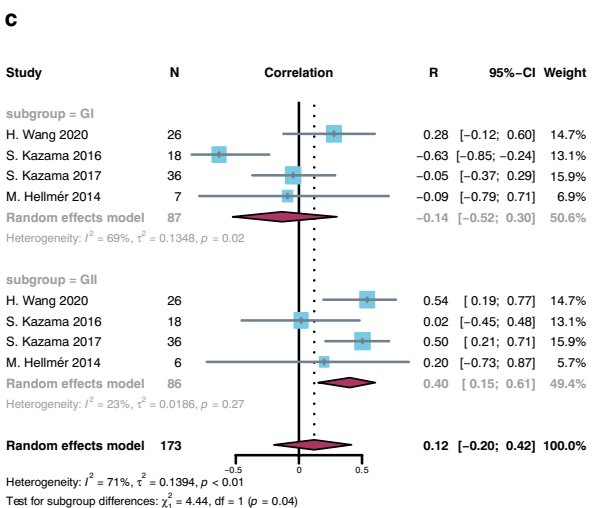
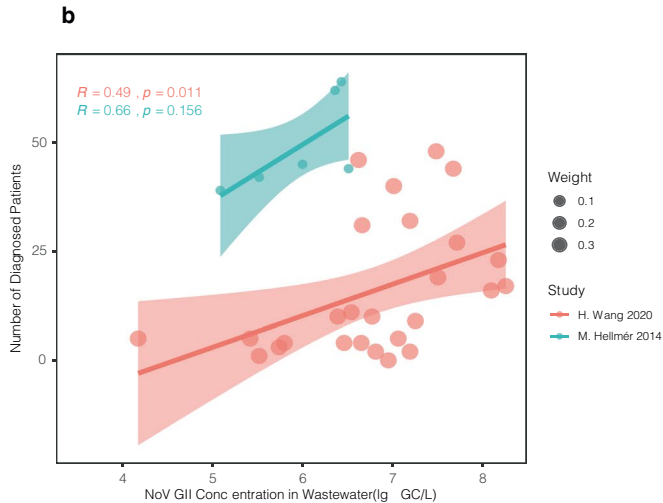
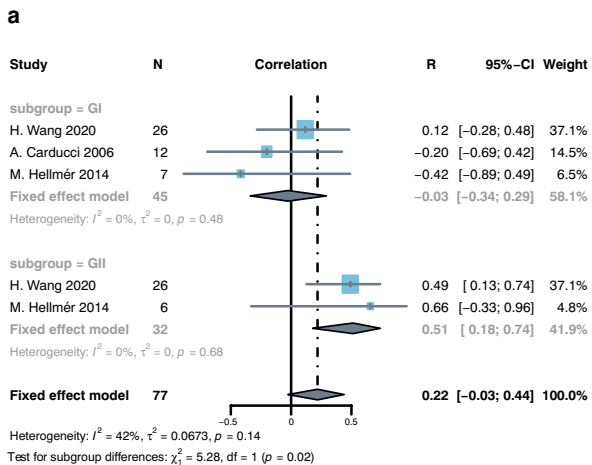


Fig. 3 Forest plots of correlation between NoV GI and GII detection in wastewater and number of **a** corresponding genogroups of AGE cases, **c** total AGE cases, and **e** outbreaks; bubble plots for correlation between NoV GII detection in wastewater and **b** GII AGE cases, **d** total AGE cases, and **f** outbreaks in each study. (For the forest plots, of concern are the respective combined results within subgroups (GI & GII). Heterogeneity exists in the correlation between NoV GI detection in wastewater and number of total AGE cases (c), using the random effects model; for the bubble plots, which showed the trends presented in data points from each study, colors represented different studies and the size of the bubbles was determined by the weights of each study.)

observation of the trends in the individual genotypes of NoV and the determination of the distribution of local characteristics and dominant genotypes.

The overall detection rate of NoV in wastewater was 82.10%, suggesting its high prevalence in the human population worldwide. NoV RNA is shed from the feces of infected people and not susceptible to degradation; therefore, NoV transmission constantly circulates between infected human populations and environmental water (Teunis et al. 2015). The results of meta-regression showed that the detection rate of NoV was associated with genogroup and country mortality: NoV GIV was less detected, and studies in high-mortality developing countries reported lower detection rates. NoV GIV is more difficult to detect in environmental, clinical, or bivalve samples, and the mechanisms of its transmission and mutation are still unclear and deserve further exploration (Kremer et al. 2011; La Rosa et al. 2012). The low detection rate of NoV in high-mortality developing countries should not be seen as a promising result; contrarily, it may indicate that bacteria and parasites were the dominant pathogens in water of low-income countries, where they contributed to the major disease burden of gastrointestinal infections, which is also consistent with the findings of previous studies (Ahmed et al. 2014). In our study, there were few studies from high-mortality developing countries, and therefore, the inadequate sample size may have led to some estimation error.

This study compared seasonal differences in the concentrations of NoV GI and GII in wastewater. An apparent seasonal pattern for GI and GII was observed, with distinct peaks during winter and spring. This characteristic has also been verified in numerous clinical studies: NoV AGE cases and outbreaks tend to occur in winter or rather the cooler months (Ahmed et al. 2013; Farkas et al. 2018; Greer et al. 2009; van Beek et al. 2018). These findings demonstrated that NoV has greater propagation and persistence in cold environments. Additionally, it may be influenced by other environmental factors such as relative humidity and latitude, as well as demographic characteristics and even infectious disease pandemic events such as the COVID-19 pandemic (Eftim et al. 2017; Oâ Reilly et al. 2021; Shamkhali Chenar and Deng 2017). It is necessary to conduct more exploration and argumentation studies.

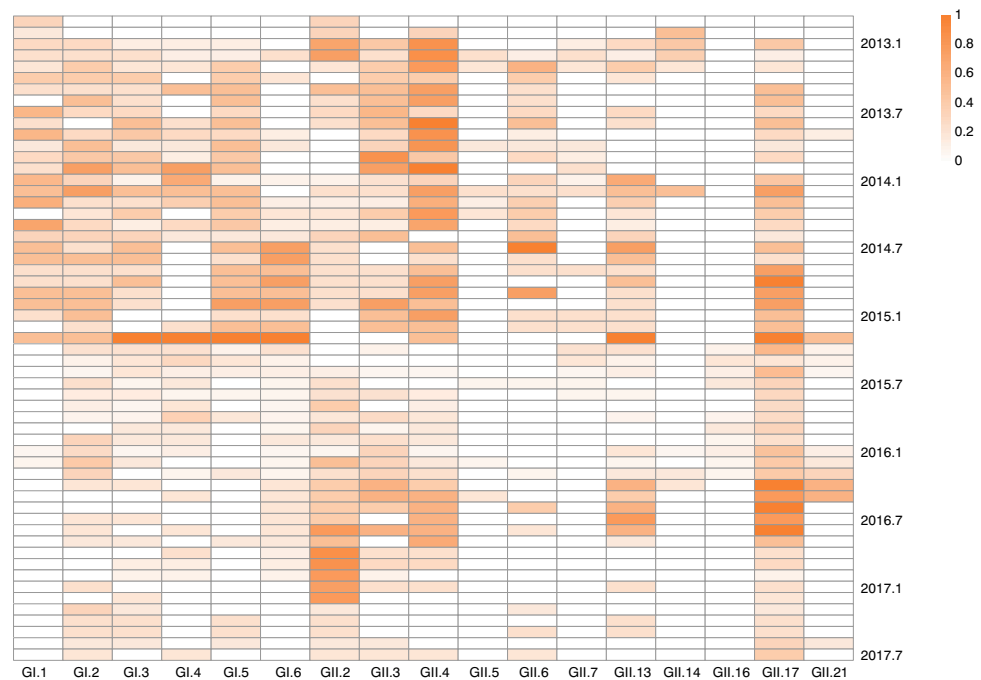
The results of the meta-analysis suggested that the concentration of NoV GII in wastewater were positively correlated with indicators reflecting AGE in the population (number of GII AGE cases, total AGE cases, and number of outbreaks). The correlation coefficients ranged from 0.40–0.51, which suggested changes in GII particles in wastewater can signify the occurrence of AGE. But for GI, no significant correlation was observed. It was impractical to establish a correlation between wastewater NoV detection and clinical cases of GI AGE infection, as GI mostly resulted in mild or asymptomatic infections, and was hard to detect in clinical surveillance. Of the NoV outbreaks, comparing GI and GII horizontally, it can be assumed that more outbreaks were caused by GII, which is consistent with the findings of clinical reports (Matthews et al. 2012; Parikh et al. 2020).

The predicted lead time provides significant evidence to prove the correlation. Kazama et al. (2017) found that the concentration of GII in sewage varied synchronously with the number of local AGE cases. By cross-correlation analysis with the data from Wang et al. (2020) study, the change in the concentration of GII was 2 weeks ahead of the occurrence of local AGE infection cases. A limitation of this result must be noted as the crude sampling frequency did not allow for calculating the lag period more precisely. However, it can still be argued that it further demonstrated the potential correlation.

This study mapped the global NoV diversity trends by bringing together numerous short-term, small-scale studies. At least 17 NoV genotypes were consistently and frequently detected in wastewater. Comparison with the genotype distribution of human AGE cases revealed relatively consistent trends, suggesting that multiple genotypes of NoV GI and GII co-circulation in the population. Several mutations of GII.4, which is the main strain causing the global NoV AGE pandemic, have been reported (Lindsmith et al. 2008; van Beek et al. 2013). Since 2012, GII.4 Sydney 2012 was the most frequently and predominantly detected strain in wastewater. For the molecular epidemiological analysis of NoV in the last five years, the GII.4 Sydney 2012 variant remains the main strain causing AGE outbreaks in most regions of the world (Cannon et al. 2021; Utsumi et al. 2021; Zhou et al. 2020).

During the winter of 2014 and 2015, several Asian countries reported that GII.17 Kawasaki was the main pathogen causing NoV AGE outbreaks (Chan et al. 2015; de Graaf et al. 2015, Matsushima et al. 2015). In fact, GII.17 was first detected before 2014 in sewage but mostly at low levels (Kazama et al. 2017; Suffredini et al. 2018) suggesting that it circulated in human populations until it became the dominant strain; molecular epidemiological studies of AGE cases in humans have also reported this finding (van Beek et al. 2018).

Fig. 4 Temporal distribution of NoV genotypes from winter 2012 to summer 2017



GII.2 was increasingly identified in wastewater surveillance studies after mid-2015. Of note, most articles assessed in this review pointed out that GII.2 predominance stemmed from the recombinant GII.2[P16] (Lu et al. 2021; Lun et al. 2018; Santiso-Bellón et al. 2020). Reports about AGE cases and outbreaks caused by GII.2[P16] have focused on clinical surveillance in various regions during the winter of 2016 and 2017 (Bidalot et al. 2017, Bonura et al. 2021; Li et al. 2018; Medici et al. 2018). The GII.P16 polymerase also paired with some other capsid genotypes, including the predominant strain GII.4 Sydney 2012. The occurrence of GII.2[P16] and GII.4 Sydney 2012[P16] suggested that recombination between such non-closely related sequences may facilitate their adaptation and transmission in the population (van Beek et al. 2018).

Since the emergence of the COVID-19 pandemic, strict social restriction measures in each country have led to a significant reduction in NoV infection (Ahn et al. 2021; Eigner et al. 2021; Lennon et al. 2020). Douglas et al. suggested that the reduction in referred NoV-positive samples and genotyping during the COVID-19 pandemic may have resulted in missing key indicators of NoV strain replacement events (Douglas et al. 2021). Therefore, there is a need to establish a sensitive and effective monitoring system to respond to possible peaks of outbreaks after the removal of restrictions.

This study had limitations. First, because of the insufficient information, we did not consider variables such as sewage sampling method (grab or composite sampling), storage temperature and duration, efficiency of the PCR assay, population size served by WWTP, and local AGE prevalence during the sampling period, which prevented us to explore

the heterogeneity of NoV detection rates in a more detailed manner. Second, the use of a value equal to the LOD divided by square root of 2 to replace values reported below the LOD may have led to the overestimation of the NoV concentration in the sewage water. Third, despite relaxing the criteria for our review, there were still too few studies reporting both NoV detection in wastewater and the gastroenteritis infection status in the population, which may result in a loss of partial representation. Furthermore, in these studies, the data reflecting the status of AGE infection included the number of clinical cases and outbreaks, rather than the local incidence or prevalence, which may have led to biased estimates.

Conclusion

Through the review of previous NoV wastewater monitoring studies, a positive correlation between NoV GII concentration in wastewater and AGE infections was observed, and cross-correlation analysis of partial data indicated that variations in GII concentration were consistent with or ahead of that in the number of AGE cases. The diversity of NoV genotypes in wastewater was also observed, and the dominant strains in the wastewater showed a consistent temporal distribution with that in human AGE cases. Our study demonstrates the potential association of NoV detection in wastewater with AGE infections in the population, and further studies are needed to confirm this conclusion.

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Author contribution All authors contributed to the study conception and design. Conceptualization: YH, NZ, and HJ; Data curation: YH, SZ, and YY; Methodology: YH, YH, ML, YH, NZ, and HJ; Formal analysis: YH, NS, and LY; Validation: QW and TC; Visualization: YH; Writing—original draft preparation: YH, NZ, and HJ; Writing—review and editing: YH, NZ, and HJ; Funding acquisition: HJ, NZ, and YH; Supervision: HJ. All authors read and approved the final manuscript.

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Availability of data and materials The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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