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 (rS = 0.51, 95% CI: 0.18–0.74, I2 = 0%), total AGE cases (rS = 0.40, 95% CI: 0.15–0.61, I2 = 23%) and NoV outbreaks (rS = 0.47, 95% CI: 0.30–0.62, I2 = 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 polyprotein, ORF2 encodes the major structural protein (VP1), and ORF3 encodes the minor structural protein (VP2). Based on the complete capsid amino acid sequences, NoVs are 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...
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 Xagoraraki 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 $\leq 1$ year, and only 4 studies were sampled for more than three years. Different methods were used for assessing the virus concentration, including adsorption-elution ($n = 16$),

![Flow diagram of included studies and the selection process](image-url)
| Author                  | Country/region | Sampling time      | Virus concentration method | PCR  | N  | GI detection rate | GII detection rate | GIV detection rate | Outcome | Genogroup | Reported seasonality | LOD (lg GC/L) |
|-------------------------|----------------|--------------------|----------------------------|------|----|------------------|-------------------|------------------|---------|-----------|---------------------|----------------|
| (Wang et al. 2020)      | Sweden         | 2016.12–2017.12    | qRT-PCR                    | 26   | 1  | 0.73             |                   |                  |          | GI, GII, GIV | Yes                 |                |
| (La Rosa et al. 2008)   | Italy          | 2007.1–2007.12     | RT-PCR                     | 75   |    | 0.1              |                   |                  |          | GIV       | No                  |                |
| (Kazama et al. 2016)    | Japan          | 2012.1–2013.3      | qRT-PCR                    | 17   | 0.82 | 0.65            |                   |                  |          | GI, GII   | Yes                 |                |
| (Kamel et al. 2010)     | Egypt          | 2006.4–2007.2      | qRT-PCR                    | 72   | 0.15 | 0.3              |                   |                  |          | GIV       | No                  |                |
| (Fioretti et al. 2018)  | Brazil         | 2013.5–2014.5      | qRT-PCR                    | 52   |    | 0.52             |                   |                  |          | GIV       | No                  |                |
| (Carducci et al. 2006)  | Italy          | 2004.5–2005.3      | qRT-PCR                    | 12   | 0.8  | 0.8              |                   |                  |          | GI, GII   | Yes                 |                |
| (Zhou et al. 2016)      | China          | 2014.1–2014.12     | qRT-PCR                    | 23   | 1.0  |                  |                   |                  |          | GI, GII   | Yes                 |                |
| (Victoria et al. 2016)  | Uruguay        | 2011.3–2013.4      | RT-PCR                     | 116  | 0.31 | 0.65             |                   |                  |          | GII       | No                  |                |
| (Victoria et al. 2010)  | Brazil         | 2005.1–2005.12     | qRT-PCR                    | 24   | 0.4  | 0.67             |                   |                  |          | GI, GII   | No                  |                |
| (Teixeira et al. 2016)  | Brazil         | 2008.11–2010.10    | RT-PCR                     | 24   | 0.17 |                  |                   |                  |          | GIV       | No                  |                |
| (Teixeira et al. 2017)  | Brazil         | 2008.11–2010.10    | RT-PCR                     | 24   | 0.79 | 0.71             |                   |                  |          | GI, GII   | No                  |                |
| (Tao et al. 2015)       | China          | 2013.1–2013.12     | RT-PCR                     | 24   | 1.0  |                  |                   |                  |          | GI, GII   | No                  |                |
| (Suffredini et al. 2018)| Italy          | 2011.1–2016.12     | RT-PCR                     | 19   | 0.84 |                  |                   |                  |          | GI        | No                  |                |
| (Skraber et al. 2011)   | Luxembourg     | 2008–2009 winters | RT-PCR                     | 78   | 0.44 | 0.97             |                   |                  |          | GI, GII   | No                  |                |
| (Prado et al. 2019)     | Brazil         | 2015.4–2016.3      | qRT-PCR                    | 12   | 0.25 |                  |                   |                  |          | GII       | No                  |                |
| (Musciello et al. 2013) | Italy          | 2011.5–2012.5      | qRT-PCR                    | 48   | 0.94 | 0.98             |                   |                  |          | GI, GII   | No                  |                |
| (Montazeri et al. 2015) | United States  | 2013.7–2014.6      | qRT-PCR                    | 12   | 0.83 | 0.83             |                   |                  |          | GI, GII   | Yes                 |                |
| (Masago et al. 2016)    | Japan          | 2012.8–2013.12     | qRT-PCR                    | 70   | 0.71 | 0.81             |                   |                  |          | GI, GII   | No                  |                |
| (Mabasa et al. 2018)    | South Africa   | 2015.4–2016.3      | qRT-PCR                    | 108  | 0.41 | 0.68             |                   |                  |          | GI, GII   | Yes                 |                |
| (La Rosa et al. 2010)   | Italy          | 2007.5–2007.9      | RT-PCR                     | 64   | 0.94 | 0.92             |                   |                  |          | GI, GII, GIV | No                  |                |
| (Kitajima et al. 2012)  | Japan          | 2005.3–2006.2      | qRT-PCR                    | 12   | 1.0  |                  |                   |                  |          | GI, GII   | Yes                 |                |
| (Kazama et al. 2017)    | Japan          | 2013–2016          | qRT-PCR                    | 156  | 0.58 | 0.79             |                   |                  |          | GI, GII   | Yes                 | GA = 4.5 GI = 4.6 |
| (Hassine-Zaafraane et al. 2014) | Tunisia    | 2007.4–2010.4     | RT-PCR                     | 309  | 0.31 | 0.1              |                   |                  |          | GI, GII   | No                  |                |
| (Haramoto et al. 2011)  | Japan          | 2003.7–2004.6      | qRT-PCR                    | 12   | 1.0  |                  |                   |                  |          | GI, GII   | Yes                 |                |
| (Han et al. 2014)       | South Korea    | 2010.12–2012.5     | RT-PCR                     | 14   | 0.36 | 0.21             |                   |                  |          | GI, GII, GIV | No                  |                |
| (Fumian et al. 2019)    | Brazil         | 2013.4–2014.5      | qRT-PCR                    | 52   | 0.38 | 0.96             |                   |                  |          | GI, GII   | Yes                 | GI = 3.9       |
| (Kobayashi et al. 2017) | Japan          | 2014.4–2015.3      | qRT-PCR                    | 25   | 1.0  | 0.4              |                   |                  |          | GI, GII   | Yes                 |                |
| (Gurung et al. 2017)    | Finland        | 2016.1–2016.4      | qRT-PCR                    | 14   | 0.71 | 1.0              |                   |                  |          | GI, GII   | Yes                 | GI = 3.90      |
| (Amarrasiri et al. 2018)| Japan          | 2013.10–2015.2     | qRT-PCR                    | 5    | 1.0  |                  |                   |                  |          | GI        | No                  |                |
| (Campos et al. 2016)    | England        | 2009.6–2011.5      | RT-PCR                     | 41   | 0.83 | 1.0              |                   |                  |          | GI, GII   | Yes                 |                |
| (Pérez-Sautu et al. 2012)| Spain        | 2007.11–2009.4     | qRT-PCR                    | 54   | 1.0  |                  |                   |                  |          | GI, GII   | Yes                 | GI = 3.55      |
| Study (Reference) | Location | Dates | Method | N | Concentration | Genotypes | Result | GI | GII | GI = | GII = |
|------------------|----------|-------|--------|---|---------------|-----------|--------|----|----|-------|-------|
| (Sima et al. 2011) | France | 2009.10–2010.6 | qRT-PCR | 31 | 0.9 | 0.84 | GI, GII | Yes | GI | GII | 2.26 |
| (Miura et al. 2015) | Japan | 2010.12–2012.3 | qRT-PCR | 16 | 0.94 | 0.94 | GI | Yes | GII | 1.25 |
| (Masclaux et al. 2013) | Switzerland | 2010–2011 summer&winter | qRT-PCR | 62 | 0.97 | 0.97 | GI | Yes | GII | 4.27 |
| (Kauppinen et al. 2014) | Finland | 2010.10–2011.10 | qRT-PCR | 19 | 0.95 | 1 | GI, GII | Yes | GI | GII | |
| (Hellmér et al. 2014) | Sweden | 2013.1–2013.5 | qRT-PCR | 7 | 0.71 | 0.86 | GI, GII | Yes | GI | 1.0 |
| (Grøndahl-Rosado et al. 2014) | Norway | 2011.1–2012.5 | qRT-PCR | 17 | 0.41 | 0.53 | GI, GII | Yes | GI | GII | 3.60 GII = 4.04 |
| (Da Silva et al. 2007) | France | 2005.12–2006.12 | qRT-PCR | 81 | 0.98 | 1 | GI, GII | Yes | GI | 3.45 GII = 2.36 |
| (Aw and Gin 2010) | Singapore | 2007.1–2007.6 | qRT-PCR | 18 | 1 | 1 | GI, GII | No | GI | 5.0 |
| (Lu et al. 2021) | China | 2013.1–2018.12 | qRT-PCR | 72 | 0.92 | 1 | GI, GII | Yes | GI | GII | 5.0 |
| (McCall et al. 2020) | United States | 2017.11–2018.2 | qRT-PCR | 18 | 0.67 | 0.86 | GI, GII | No | GI | 5.0 |
| (Lin et al. 2021) | China | 2014–2016 | RT-PCR | 36 | 1 | 1 | GI, GII | No | GI | 5.0 |
| (Santiso-Bellón et al. 2020) | Spain | 2016.9–2017.9 | qRT-PCR | 46 | 0.7 | 0.76 | GI, GII | No | GI | GII | No |
| (Ibrahim et al. 2020) | Tunisia | 2018.6–2019.4 | qRT-PCR | 20 | 0.85 | 1 | GI, GII | Yes | GI | GII | |
| (Lun et al. 2018) | Australia | 2014.7–2016.12 | RT-PCR | 12 | 1 | 1 | GI, GII | No | GI | GII | |

*a*1 Adsorption-extraction; 2 Polyethylene glycol precipitation; 3 Ultrafiltration; 4 Elution and skimmed-milk flocculation procedure; 5 Ultracentrifugation; 6 Other methods

*b*1 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 multifactor 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).
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 GI 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 GI 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 GI.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...
### Study Results

#### Fixed effect model

**Heterogeneity:** $I^2 = 42\%$, $τ^2 = 0.0673$, $p = 0.14$

**Test for subgroup differences:** $χ^2 = 5.28$, df = 1 ($p = 0.02$)

- **Subgroup: GI**
  - H. Wang 2020: $R = 0.22$, 95% CI: $[−0.03; 0.44]$, $p = 0.14$
  - M. Hellmér 2014: $R = 0.50$, 95% CI: $[0.13; 0.74]$, $p = 0.0001$

- **Subgroup: GII**
  - A. Carducci 2006: $R = 0.49$, 95% CI: $[−0.03; 0.44]$, $p = 0.14$
  - S. Kazama 2016: $R = 0.47$, 95% CI: $[−0.69; 0.42]$, $p = 0.18$

**Fixed effect model**

**Heterogeneity:** $I^2 = 0\%$, $τ^2 = 0$, $p = 0.68$

- **Subgroup: GI**
  - H. Wang 2020: $R = 0.12$, 95% CI: $[−0.12; 0.60]$, $p = 0.14$
  - M. Hellmér 2014: $R = 0.50$, 95% CI: $[−0.03; 0.44]$, $p = 0.14$

- **Subgroup: GII**
  - A. Carducci 2006: $R = 0.49$, 95% CI: $[−0.03; 0.44]$, $p = 0.14$
  - S. Kazama 2016: $R = 0.47$, 95% CI: $[−0.69; 0.42]$, $p = 0.18$

**Random effects model**

**Heterogeneity:** $I^2 = 71\%$, $τ^2 = 0.1348$, $p = 0.02$

- **Subgroup: GI**
  - H. Wang 2020: $R = 0.12$, 95% CI: $[−0.20; 0.42]$, $p = 0.02$
  - M. Hellmér 2014: $R = 0.50$, 95% CI: $[−0.03; 0.44]$, $p = 0.14$

- **Subgroup: GII**
  - A. Carducci 2006: $R = 0.49$, 95% CI: $[−0.03; 0.44]$, $p = 0.14$
  - S. Kazama 2016: $R = 0.47$, 95% CI: $[−0.69; 0.42]$, $p = 0.18$

**Fixed effect model**

**Heterogeneity:** $I^2 = 0\%$, $τ^2 = 0$, $p = 0.86$

- **Subgroup: GI**
  - H. Wang 2020: $R = 0.12$, 95% CI: $[−0.20; 0.42]$, $p = 0.02$
  - M. Hellmér 2014: $R = 0.50$, 95% CI: $[−0.03; 0.44]$, $p = 0.14$

- **Subgroup: GII**
  - A. Carducci 2006: $R = 0.49$, 95% CI: $[−0.03; 0.44]$, $p = 0.14$
  - S. Kazama 2016: $R = 0.47$, 95% CI: $[−0.69; 0.42]$, $p = 0.18$

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### Correlation

**R**

| Study              | N  | Correlation | 95% CI          | Weight |
|--------------------|----|-------------|-----------------|--------|
| H. Wang 2020       | 26 | 0.22        | [−0.03; 0.44]   | 100%   |

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### Diagrams

**a**

- **Study:** Campos, C. J. A 2016
  - **GII** concentration in wastewater (lg GC/L)
  - **Number of AGE diagnosed patients**

**b**

- **Study:** H. Wang 2020
  - **NoV GII concentration in wastewater** (lg GC/L)

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**c**

- **Study:** Campos, C. J. A 2016
  - **GII** concentration in wastewater (lg GC/L)
  - **Number of AGE diagnosed patients**

**d**

- **Study:** H. Wang 2020
  - **NoV GII concentration in wastewater** (lg GC/L)

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**e**

- **Study:** Campos, C. J. A 2016
  - **GII** concentration in wastewater (lg GC/L)
  - **Number of AGE diagnosed patients**

**f**

- **Study:** Campos, C. J. A 2016
  - **NoV GII concentration in wastewater** (lg GC/L)
and argumentation studies. It is necessary to conduct more exploration (Eftim et al. 2017; O’Reilly et al. 2021; Shamkhali Chenar et al. 2009; van Beek et al. 2018). These findings demonstrated the potential 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 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; Ò 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 GI 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 GI.4, which is the main strain causing the global NoV AGE pandemic, have been reported (Lindesmith et al. 2008; van Beek et al. 2013). Since 2012, GI.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 GI.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 GI.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, GI.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).
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; Funding acquisition: HJ, NZ, and YH; 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.

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