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Localised wastewater SARS-CoV-2 levels linked to COVID-19 cases: A long-term multisite study in England

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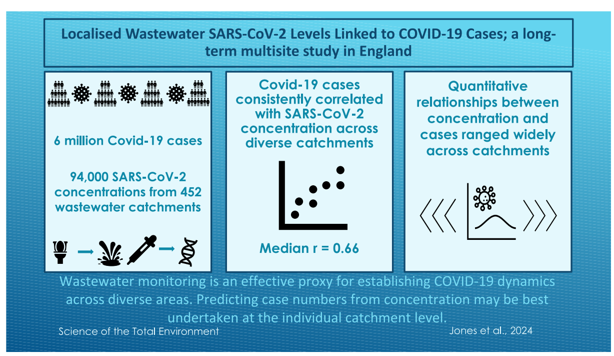
HIGHLIGHTS

- SARS-CoV-2 concentration in wastewater correlates with COVID-19 in the community.
- Despite methodological uncertainties correlations show consistency across sites.
- The prediction of cases from concentration is highly variable.
- Catchment characteristics do not impact on the case concentration relationship
- Wastewater monitoring can be used to establish the dynamics of community COVID-19.

GRAPHICAL ABSTRACT



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ABSTRACT

Wastewater-based surveillance (WBS) can monitor for the presence of human health pathogens in the population. During COVID-19, WBS was widely used to determine wastewater SARS-CoV-2 RNA concentration (concentrations) providing information on community COVID-19 cases (cases). However, studies examining the relationship between concentrations and cases tend to be localised or focussed on small-scale institutional settings. Few have examined this relationship in multiple settings, over long periods, with large sample numbers, nor attempted to quantify the relationship between concentrations and cases or detail how catchment characteristics affected these.

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This 18-month study (07/20–12/21) explored the correlation and quantitative relationship between concentrations and cases using censored regression. Our analysis used >94,000 wastewater samples collected from 452 diverse sampling sites (259 Sewage Treatment Works (STW) and 193 Sewer Network Sites (SNS)) covering ~65 % of the English population. Wastewater concentrations were linked to ~6 million diagnostically confirmed COVID-19 cases.

High correlation coefficients were found between concentrations and cases (STW: median r = 0.66, IQR: 0.57–0.74; SNS: median r = 0.65, IQR: 0.54–0.74). The quantitative relationship (regression coefficient) between concentrations and cases was variable between catchments. Catchment and sampling characteristics (e.g. size of population and grab vs automated sampling) had significant but small effects on correlation and regression coefficients.

During the last six months of the study correlation coefficients reduced and regression coefficients became highly variable between catchments. This coincided with a shift towards younger cases, a highly vaccinated population and rapid emergence of the variant Omicron.

The English WBS programme was rapidly introduced at scale during COVID-19. Laboratory methods evolved and study catchments were highly diverse in size and characteristics. Despite this diversity, findings indicate that WBS provides an effective proxy for establishing COVID-19 dynamics across a wide variety of communities. While there is potential for predicting COVID-19 cases from wastewater concentration, this may be more effective at smaller scales.

1. Introduction

Wastewater-based surveillance (WBS) is a method of testing wastewater for the presence of pathogens and chemicals associated with human and animal health. Originally used to survey for poliovirus (Metcalf et al., 1995), it further developed to assess drug use in populations (Van Nuijs et al., 2011). Subsequently, WBS broadened to include monitoring for the presence of circulating pathogens, and estimating the extent of infectious disease in populations (Kilaru et al., 2023). During the COVID-19 pandemic, WBS was part of a suite of systems used to assess SARS-CoV-2 infections in populations (Brainard et al., 2023; Ciannella et al., 2023) and its use became globally widespread (Naughton et al., 2023).

The quantity of SARS-CoV-2 RNA in wastewater has been used to estimate COVID-19 prevalence in the population from which the wastewater is sampled (Barcellos et al., 2023; Zahedi et al., 2021; Tiwari et al., 2022). For WBS, samples are generally taken from large-scale treatment works and smaller-scale sewer network sites (Liu et al., 2022), not small private sewage systems such as septic tanks. Sampling methods include the grab method, where a sample is taken at a single time point, and the composite method, where multiple samples are taken semi-continuously and pooled to form a sample representing a specific period of time, typically a 24-h period (US EPA, 2013). The composite method is generally conducted at sewage treatment works where power and good access exist. In contrast the grab method is often utilised along the sewer network system (e.g. inspection chambers located in roads). The composite method can be more representative of COVID-19 prevalence than the grab method (Liu et al., 2022) but is typically more expensive. The concentration of SARS-CoV-2 is determined by quantifying the number of gene copies per litre of wastewater (gc/l) (UKHSA, 2022b).

WBS presents some advantages to more traditional clinical surveillance methods, as it is non-invasive and potentially permits the monitoring of all virus shedding individuals, regardless of their symptom or tested status (e.g. pre-symptomatic, symptomatic, asymptomatic, tested or untested cases) (Bonanno Ferraro et al., 2022). In addition, because individuals may shed SARS-CoV-2 in faeces and urine before becoming symptomatic, it can provide an early indication of disease epidemiology (Gitter et al., 2022), including presence of novel variants, and complement clinical surveillance of populations (Bonanno Ferraro et al., 2022). To ensure WBS provides accurate insights, it is necessary to understand how wastewater concentrations relate to levels of, and trends in COVID-19 in the population (Kilaru et al., 2023).

Previous studies have investigated the presence of SARS-CoV-2 in wastewater and correlated this with clinically confirmed cases (see Li et al. (2023) and Bonanno Ferraro et al. (2022) for reviews), with some attempting to predict COVID-19 case numbers from SARS-CoV-2 concentrations in wastewater (e.g. Kisand et al., 2023; Fitzgerald et al., 2021; López-Peñalver et al., 2023). Many studies focused on closed/semi-closed institutions such as university campuses (e.g. Lu et al., 2022; Scott et al., 2021; Wright et al., 2022), airports (e.g. Nkambule et al., 2023; Van Der Drift et al., 2024), prisons (e.g. Jobling et al., 2024; Klevens et al., 2023) and hospitals (e.g. De Araújo et al., 2023; Acosta et al., 2023; Hong et al., 2021) and not the entire population at risk.

A smaller proportion of studies focused on community settings. These were often based on small neighbourhood clusters (e.g. De Graaf et al., 2023; Acosta et al., 2022), individual municipalities (e.g. Hopkins et al., 2023; Belmonte-Lopes et al., 2023) or small groupings of communities or municipalities (e.g. Hasing et al., 2023; Fernandez-Cassi et al., 2021). A few studies examined larger communities, such as regions within countries (e.g. D'Souza et al., 2024; Fitzgerald et al., 2021; Duvallet et al., 2022), of which just three sampled data over a year or more (Wadi et al., 2023; Kisand et al., 2023; Janssens et al., 2022). The number of sampling sites (either SNS or STW) included in studies varied, from fewer than 10 sites (e.g. 3 sites Acosta et al., 2022, 9 sites Hasing et al., 2023) to hundreds of sites (e.g. 244 sites D'Souza et al., 2024, 453 sites Wadi et al., 2023). A limitation of many of these studies is that, although they investigate the strength of the relationship between SARS-CoV-2 concentration in wastewater and clinical cases of COVID-19, there is little attempt to quantify these relationships or investigate whether and, if so, why relationships may vary between different wastewater sites. This is in spite of studies that have examined the impact of, for example, various demographic factors on SARS-CoV-2 concentrations in wastewater (e.g. Acosta et al., 2022; Li et al., 2022) and cases (e.g. Lancaster et al., 2022; Nelson et al., 2022).

Here we investigate the relationship between SARS-CoV-2 concentrations in wastewater, measured as part of the Environmental Monitoring for Health Protection (EMHP) SARS-CoV-2 wastewater monitoring programme (e.g. UKHSA, 2022b), and confirmed cases of COVID-19 across England. The EMHP was rapidly introduced at scale during the COVID-19 pandemic. We examine the strength of association (correlation) and the quantitative relationship (regression coefficients). We use a dataset of 94,530 wastewater samples from 452 highly diverse (in terms of geographical size and associated environmental and social characteristics) wastewater catchments (geographical areas contributing sewage to the wastewater site), sampled over 18 months (July 2020 to December 2021). This wastewater data was matched to over 6 million COVID-19 cases, each with an individual address. We explore the correlation and regression coefficients between SARS-CoV-2 concentrations in wastewater and COVID-19 cases in the population and how these differ between sites. We examine the potential impact of the environmental and social characteristics of the wastewater catchments and the sampling methods used. To the best of our knowledge this is one of the largest investigations into the relationship between wastewater surveillance data and COVID-19 cases and one of the first to look at understanding differences between wastewater catchments.

2. Methods

2.1. Study period

Wastewater surveillance for SARS-CoV-2 was undertaken in England from July 2020 (Wade et al., 2022; Defra/JBC, 2020) until March 2022 (UKHSA, 2022b). The recording of population-wide COVID-19 cases in England began in April 2020 (DHSC, 2020) and ran until the beginning of 2022, when community mass testing was scaled down (UKHSA, 2022d). This study focussed on the 18-month period from 15th July 2020 to 19th December 2021 and covers the time when surveillance of both SARS-CoV-2 in wastewater and population-wide COVID-19 cases occurred.

2.2. Wastewater concentration data

In July 2020, the Joint Biosecurity Centre (JBC) began monitoring the concentration of SARS-CoV-2 in wastewater from sewage treatment works (STW) and sewer network sites (SNS) (together "wastewater sites") across England. STW are centralised systems where sewage is treated to remove contaminants and typically cover large wastewater catchments such as towns or cities. SNS connect the treatment plants with the communities they serve, are often accessed by inspection chambers or at pumping stations, and represent a subsection of the larger catchment (UKHSA, 2022c). SARS-CoV-2 concentration data was obtained from 491 wastewater sites (271 STW and 220 SNS) with valid geographical catchments and data within the study period. To estimate relationships between SARS-CoV-2 concentrations and case numbers it is important that a sufficiently long period is examined. Hence, wastewater sites were only included if they covered at least 180 days of wastewater concentration data, which excluded 39 sites. Final analysis used data from 452 wastewater sites (259 STW and 193 SNS), representing all regions of England and ~ 65 % of the English population.

The wastewater catchment boundaries, showing the geographical area contributing sewage to the wastewater site, for each STW and SNS were obtained from UKHSA, having been provided by water companies. All wastewater catchments were considered constant throughout the study. Fig. 1a shows the locations of the STW wastewater catchments and Fig. 1b the SNS wastewater catchments. There was some geographical overlap between STW and SNS. Around 73 % of SNS catchment areas overlapped with STW catchments and 21 % of STW overlapped with SNS catchment areas. In cases where there was some overlap of boundaries the dates of wastewater sampling were frequently different between the overlapping STW and the SNS catchments (see below). Consequently, data for SNS and STW were examined independently and not pooled. The distribution of wastewater catchments broadly reflects the population density of England.

Wastewater sites were not consistently sampled during the study period. Sampling increased over time as the EMHP wastewater monitoring programme for SARS-CoV-2 was scaled up from late 2020 (Wade et al., 2022). Of the 452 included sites, the earliest sampling date was 15th July 2020 (start of the SARS-CoV-2 wastewater monitoring programme), with the last site introduced on 21st June 2021. Similarly, not all sites were sampled until the end of the project; the earliest end date used in this study was 6th July 2021. The length of time between the first sampling date and the final sampling date ranged from 182 to 523 days. Altogether, 38 sites (all STW) had wastewater concentration data over

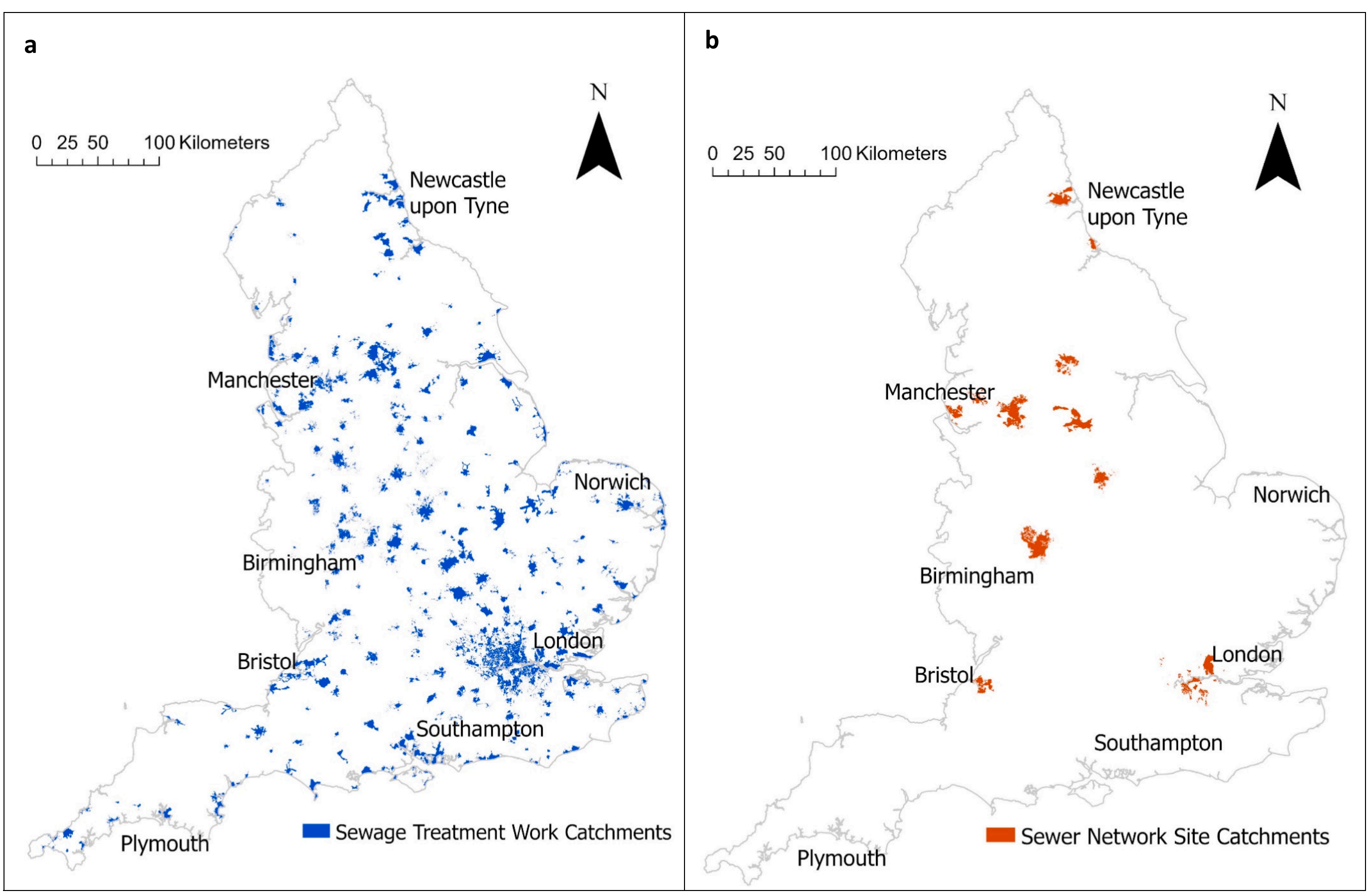

Fig. 1. Sewage treatment work and sewer network site catchment locations across the EMHP wastewater monitoring programme in England.

the entire period (albeit not daily). The number of days samples were taken from each site also varied. SNS samples were collected approximately four times a week while samples from STW were taken approximately three times a week (UKHSA, 2022c). Grab sampling occurred more frequently at SNS. In total 94,530 wastewater samples were included in the study, 42,237 from STW and 52,293 from SNS.

Within each of the 452 sites, the presence of SARS-CoV-2 in wastewater was determined by a measure of the concentration of the nucleocapsid gene (N1), obtained using quantitative reverse transcription PCR (qRT PCR). The number of SARS-CoV-2 N1 gene copies per litre of wastewater (gc/l) was estimated, with concentration of SARS-CoV-2 adjusted using median of flow estimates calculated from an in-house JBC model accounting for changes in levels of multiple markers such as ammonia and orthophosphate. The scale of the EMHP programme necessitated the use of multiple Environment Agency laboratories across England for analysis, while the rapid introduction of the programme in the early stages of the pandemic resulted in the continuous assessment and improvement of laboratory methods in this evolving field. While the development of methods used to obtain concentration was ongoing during the data collection period of this study, a method utilising viral precipitation by polyethylene glycol was used for the majority of the study across all laboratories (Farkas et al., 2021; Walker, 2022). Further details of the laboratory methods used to obtain SARS-CoV-2 concentrations in wastewater, including flow normalisation, has been published elsewhere (UKHSA, 2022b; Farkas et al., 2021; Walker, 2022). Concentrations are daily values for the day of sampling. In interpreting the wastewater concentration data, it is critical to recognise that some of the sample values were censored, where the measured SARS-CoV-2 was below the limit of detection (LOD). Altogether 36 % of samples were below the LOD. Across sites the proportion of samples below LOD ranged between 0 % and 88 %. For each site the percentage of samples obtained by either grab or composite sampling was calculated.

2.3. Population-wide COVID-19 case data

During COVID-19, microbiology and virology National Health Service (NHS) (public), government (public) and private laboratories undertook PCR testing for SARS-CoV-2. All PCR testing results were reported to the UK Health Security Agency (UKHSA) Second Generation Surveillance System (SGSS) (Bray et al., 2024). In addition, self-reported lateral flow tests (LFT) were included in SGSS from late 2020. Each individual test reported by one person was considered a case. Individual COVID-19 case data contained a date of testing and an address. The address provided was accepted as the location of the case at time of infection. Most cases were matched to a valid address, those without an address were excluded from analysis. All valid positive COVID-19 cases were obtained from SGSS over the study period. This consisted of over 9.8 million COVID-19 cases.

2.4. Matching COVID-19 case data to wastewater catchments

All COVID-19 cases were assigned a Unique Property Reference Number using the Ordnance Survey AddressBase Premium database (OS, 2022), providing [X,Y] address location. Using GIS, cases were matched to the wastewater catchment they were located within. From the 9.8 million COVID-19 cases, 5.9 million intersected a STW catchments and 2.4 million intersected SNS catchments. Following this matching exercise, each of our 452 wastewater catchments had a daily time-series of COVID-19 cases.

2.5. Wastewater catchment characteristics

To characterise each catchment, information for Lower Super Output Areas (LSOA) were obtained. These are geographical areas of 400 to 1200 households, with populations between 1000 and 3000 people that are relatively homogenous. They are the smallest geographical unit for which socioeconomic data is available in England. For LSOAs, we obtained information on the Indices of Deprivation 2019 (UK Government National Statistics, 2019), Urban/Rural classification (UK Government Official Statistics, 2021), Ethnic group distribution (UK Census Data, 2011) and 2019 population (ONS, 2019). Using GIS, LSOA centres within wastewater catchments were identified. Fifteen wastewater sites (all SNS with small catchments) did not have an LSOA centre within and so were allocated to their nearest LSOA. Many wastewater catchments had multiple LSOA centres within and the data was summarised to encompass all LSOAs. All geographical analysis was undertaken in ArcGISPro 2.6.0 (Esri, USA).

2.6. Analysis

Across all sites, a daily log(10) SARS-CoV-2 concentration (concentration) and a daily log(10) rolling 7-day mean of cases (cases) were calculated. All cases had 0.14 added to their value (equivalent of one case in 7 days) to overcome the log0 problem. The 7-day rolling mean of cases was the mean of the measure for that date plus the previous six days. Rolling averages are commonly used in disease reporting to smooth out daily variations, known reporting artefacts of daily health surveillance data. They provide a clearer picture of changes in disease prevalence (Buckingham-Jeffery et al., 2017). Across all sites there was an estimate of cases for all days but only a concentration for days when sampling occurred.

When quantifying the relationship between cases and concentration it was critical to account for the censored wastewater data (LOD). Censored regression is a method that allows values above or below a limit to be incorporated, reducing loss of data (UCLA, 2024). Censored regression was undertaken between concentrations and cases within each catchment. From this regression McKelvey & Zavoina's R^2 was extracted as the appropriate pseudo R^2 measure for censored regression (Veall and Zimmermann, 1996). The square root of McKelvey & Zavoina's R^2 was taken to determine the degree to which the SARS-CoV-2 concentrations were correlated with COVID-19 cases. The regression coefficient was recorded as this quantifies the specific relationship between wastewater SARS-CoV-2 concentrations and COVID-19 cases in each wastewater catchment.

Each wastewater catchment varied in the length of time SARS-CoV-2 concentration data were collected. To ensure this was not influencing our results, a sub-analysis was undertaken, determining the correlation and regression coefficient values for the 38 wastewater catchments (all STW) that had data across the entire monitoring period (15th July 2020 to 19th December 2021). To explore potential changes over time, data from these 38 wastewater catchments were divided into three approximately equal time periods – 15th July 2020 to 14th January 2021 (Time 1); 15th January 2021 to 14th July 2021 (Time 2); 15th July 2021 to 19th December 2021 (Time 3). These were chosen as equal periods of time within the available data, rather than reflecting variant waves. The dominant variants for each period were Wild Type (Time 1), Alpha into Delta (Time 2) and Delta into Omicron (Time 3). Within each of these periods, correlation and regression coefficients were calculated for each wastewater catchment.

Finally, for the 452 wastewater catchments, the relationships between the correlation and regression coefficients and both the wastewater catchment characteristics and the sampling characteristics were examined using scatter plots and, if appropriate, regression analysis. All analysis was undertaken in Stata/MP 17 (StataCorp. LLC, USA).

3. Results

3.1. Wastewater catchment characteristics

The wastewater catchments were highly diverse and varied in their characteristics. A summary of their characteristics is presented in Table 1. STW catchments were 38 km^2 on average, while SNS

Table 1
Wastewater catchment characteristics.

	STW (n = 259)		SNS (n = 193)	
	Mean (SD)	Median (range)	Mean (SD)	Median (range)
Area (km^2)	38.06 (45.01)	23.76 (2.34–290.66)	14.97 (36.81)	3.94 (0.01–337.05)
Population	136,057 (277,931)	57,774 (2694–2,996,719)	69,280 (185,867)	19,177 (1163–1,667,905)
Percentage of site that is urban	88.46 (21.16)	95.45 (0–100)	97.75 (13.56)	100 (0–100)
Average index of deprivation rank[a]	16,842 (5122)	16,474 (3157–29,084)	12,409 (7766)	11,511 (216–31,551)
Percentage of population that is White British	87.64 (11.05)	91.09 (35.63–97.9)	74.45 (21.57)	82.3 (9.59–97.98)
Percentage of population that is Asian British/ Asian	4.78 (6.13)	1.95 (0.13–35.08)	10.94 (13.22)	6.34 (0–73.99)
Percentage of population that is Black British/ African/ Caribbean	1.41 (2.50)	0.55 (0.03–20.65)	5.05 (6.28)	2.66 (0.07–42.98)
Total number of days samples were collected	163.08 (46.83)	151 (77–288)	270.95 (33.86)	286 (143–320)
Average number of days samples were collected per week	3.55 (0.30)	3.64 (2.28–3.92)	5.64 (0.45)	5.77 (3.26–6.73)
Number of days from date of first sampling to date of last sampling	322.59 (92.36)	291 (181–522)	337.38 (39.51)	347 (183–412)
Percentage of samples collected using grab method	63.41 (41.83)	97.44 (0–100)	96.09 (16.88)	99.62 (2.11–100)

[a] Low values = more deprived, high values = less deprived.

catchments were smaller (15 km^2), but the latter's size was more varied (0.01km^2 to 337km^2 compared with 2km^2 to 290km^2). On average STW catchments had larger populations (mean 136,057) and showed a wider range of population (2694 to almost 3 million) compared to SNS catchments (mean 69,280, range 1163 to 1.7 million).

STW and SNS catchments had a greater proportion of urban areas than the 83 % of all English LSOAs (UK Government Official Statistics, 2021) with STW 88 % urban and SNS 98 % urban. SNS catchments were more varied in terms of their deprivation than STW catchments, with the IMD rank of SNS catchments ranging from 216 (more deprived) to 31,551 (less deprived), compared to 3157 to 29,084. SNS catchments also had median deprivation rank of 11,511, lower than the 16,474 of STW catchments which was close to the English average deprivation rank of 16,423 (UK Government National Statistics, 2019).

STW catchments had a mean White British population of 88 %, slightly higher than the English average of 85 % (ONS, 2023a), while SNS catchments had a lower value (74 %). STW had an average Asian British/Asian population of 4.78 % and an average Black British/Black/ African/Caribbean population of 1.41 %, both lower than the English averages of 7.8 % and 3.5 % respectively (ONS, 2023a), while SNS had minority ethnic populations higher than the English average (Asian British 10.94 %, Black British 6.34 %).

The median total number of days samples were collected was 151 in STW compared to 286 days in SNS, while the median length of time samples were collected for was 291 days in STW and 347 days in SNS. The weekly number of days samples were collected for was lower in STW (3.64) than SNS (5.77). In both site types, on average, most samples were collected using the grab method (STW 97.4 %, SNS 99.6 %).

3.2. *Correlations between SARS-CoV-2 concentrations in wastewater and COVID-19 cases in population*

Fig. 2 presents the distribution of correlation coefficients (r) between concentrations and cases for STW and SNS. The correlations were similar between STW and SNS, ranging from −0.07 to 0.86 in STW and − 0.44 to 0.85 in SNS. The STW median was 0.66, (IQR 0.57–0.74) and the SNS median was 0.65 (IQR 0.54–0.74) indicating low variability around the median values in both types of wastewater site. One of each site type showed negative correlation coefficients, but few clues as to the reasons for these negative correlations were found. When the analysis was restricted to wastewater catchments sampled across the whole period

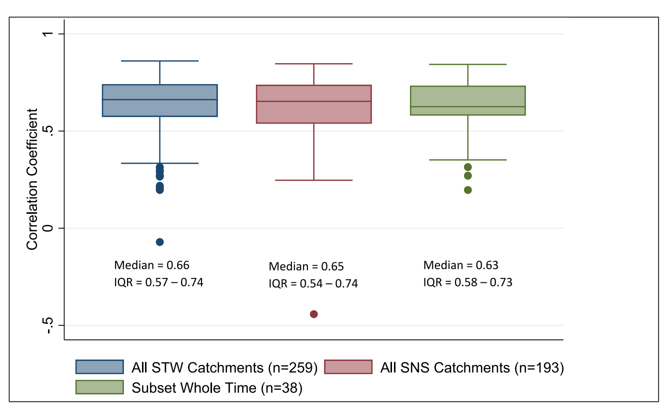

Fig. 2. Distribution of correlation coefficients (r) between log(10) SARS-CoV-2 concentrations in wastewater and log(10) COVID-19 cases in the monitored population.

(STW only), similar results emerged (Fig. 2).

3.3. Regression coefficients between SARS-CoV-2 concentrations in wastewater and COVID-19 cases in population

Box plots of the regression coefficients (unstandardised B) that describe the distributions of the slopes of the relationship between concentrations and cases in STW and SNS are shown in Fig. 3. Two coefficients were negative, one SNS and one STW, which was also a large outlier (B = -13.7). The STW median coefficient value was 0.69 (IQR 0.57–0.82), while for SNS the median equalled 0.43 (IQR 0.34–0.50). When analysis was restricted to wastewater catchments sampling across the whole period (STW only) the median and IQR were higher (0.90, IQR 0.74–1.02) than all STW and all SNS.

3.4. Correlations and regression coefficients between SARS-CoV-2 concentrations in wastewater and COVID-19 cases in population over time

Focusing on the 38 sites with SARS-CoV-2 concentration data over the whole period, Fig. 4 shows how the distributions of the correlation coefficients between concentrations and cases varied across three time periods. The distributions and percentiles for all three periods were different, with no overlapping IQRs, although the first two periods were more like each other than the third. Time 1 showed strong correlations (median r 0.80, IQR 0.74–0.86), while Time 2 displayed moderate correlations (median r 0.58, IQR 0.48–0.64). Time 3 showed weak correlations (median r 0.05, IQR -0.05–0.14).

Examining the distributions of the regression coefficients across the three time periods (Fig. 5), the first two periods had similar distributions. The median of Time 1 was 0.78 (IQR 0.71–0.95), while the Time 2 median equalled 0.65, with an IQR that overlapped Time 1 (IQR 0.56–0.87). Time 3 had a very different distribution, although the median coefficient was similar (B = 0.73) the IQR was much wider (IQR -0.85–1.77) and there were large outliers.

3.5. Relationship between site and sampling characteristics and correlation and regression coefficients

To understand the factors underlying the variability in correlation coefficients between concentrations and cases, scatterplots of correlation coefficients against explanatory variables for both STW and SNS were drawn showing that catchment and sampling characteristics had minor impacts on correlation coefficients (Supplementary material Fig. 1). Multiple regression analysis indicated index of multiple deprivation, percentage of white British in the population and average days per week samples were collected were significantly associated with STW, while log(10) area and index of multiple deprivation were associated with SNS (Supplementary material Table 1).

Scatterplots between the regression coefficients and the catchment and sampling characteristics for both STW and SNS indicated many of these factors have a small impact (Supplementary material Fig. 2). In a multiple regression analysis, significant associations between log(10) area, white British population, and percentage of grab samples were found with STW, and log(10) area and percentage of grab samples were significantly associated with SNS.

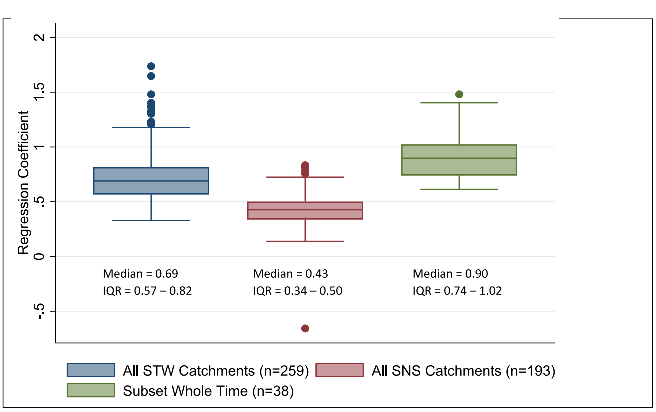

Fig. 3. Distribution of regression coefficients (unstandardised B) between log (10) SARS-CoV-2 concentrations in wastewater and log(10) COVID-19 cases in the monitored population.
(Note: outlier All STW catchments (−13.7) excluded from this figure for display purposes.)

4. Discussion

Wastewater-based surveillance (WBS) is one of a suite of systems used to assess SARS-CoV-2 infections in populations (Brainard et al., 2023). In this study we examined the relationship between the concentration of SARS-CoV-2 in wastewater, determined through WBS adjusted for multiple markers, and monitored cases of COVID-19 across England over an 18-month period. Previous studies have examined the use of WBS to determine the relationship between concentration of SARS-CoV-2 in wastewater and cases of COVID-19 (see the review Li et al., 2023), however previously published studies cover shorter time periods (e.g. Duvallet et al., 2022; D'Souza et al., 2024) and smaller geographical ranges, (e.g. De Graaf et al., 2023; Hasing et al., 2023). Some investigated similar timescales and geographies (e.g. Belgium, 15 months: Janssens et al., 2022, Estonia, 17 months: Kisand et al., 2023, and UAE, 26 months: Wadi et al., 2023). However, these are countries with smaller populations than England and, importantly, focus on much lower numbers of wastewater catchments (e.g., Belgium - 42; Estonia - 20). The UAE study covered a similar number of wastewater sites (453 over 26 months) but only included 16,858 samples, <20 % of the samples included here.

In spite of the rapid introduction of the England wastewater monitoring programme, across all the wastewater catchments (259 STW, 193 SNS), there was constant positive correlation between log(10) COVID-19 cases and log(10) SARS-COV-2 concentration in wastewater (median r STW = 0.66; SNS = 0.65). This was retained across the 38 STW sites that had data for the whole period. Although similar correlations have been found elsewhere (Fitzgerald et al., 2021; Duvallet et al., 2022; Wadi et al., 2023), the consistency in correlation coefficients across all wastewater catchments was unexpected. Given the different type of sites (STW and SNS) and the large diversity in catchment and sampling characteristics, greater variation across results might have been expected. Sampling at STWs has traditionally be used to assess a pathogen across large or multiple neighbourhoods (Bowes et al., 2022), while samples from SNS have tended to be more targeted to specific communities (Yeager et al., 2021). We choose not to pool findings from STW and SNS due to potential differences in wastewater origin and some limited overlap between some sites. However, our findings show that the two sources produced consistent results, suggesting wastewater samples from STW and SNS are presenting the same information.

Associations between the correlations and catchment and sampling characteristics showed some significant relationships, but the magnitude of effects were small. The multiple regression indicated that more deprived catchments (STW and SNS) have slightly lower r values. For STW, increasing proportions of non-white population also lowered r values. Both these may be due to behavioural or reporting factors (Green et al., 2021). For SNS smaller catchments had a lower r value, an effect not seen in STW, likely because there were few small STW catchments (e.g. none $<1km^2$). More frequent sampling increased r value in STW an effect not seen in SNS. However, SNS were on average sampled with greater frequency. Given studies have shown variations in the concentration of SAR-CoV-2 in wastewater determined using different sampling methods (composite and grab) (Wade et al., 2022), the relatively low importance of sampling methods was somewhat surprising and may relate to the high abundance of COVID-19 in the population during this

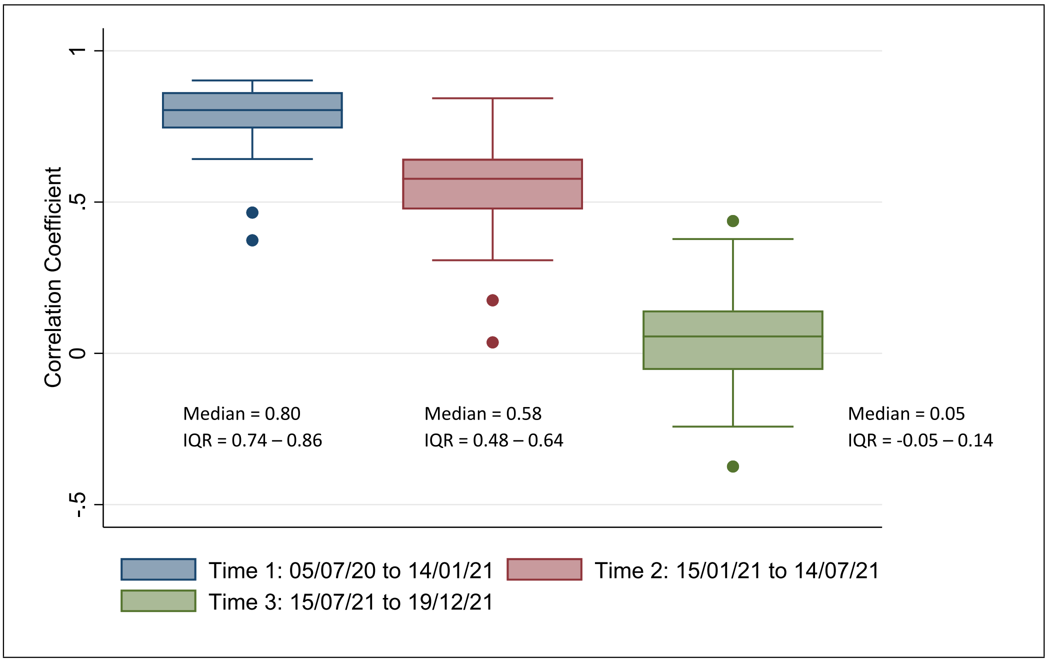

Fig. 4. Distribution of correlation coefficients (r) between log(10) SARS-CoV-2 concentrations and log(10) COVID-19 cases in the monitored population over time (n = 38).

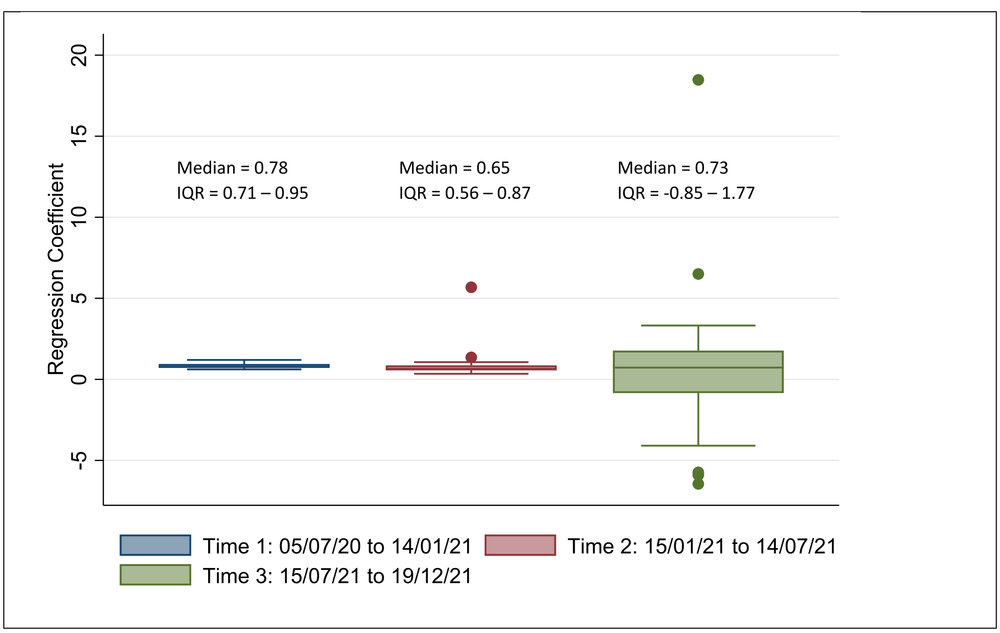

Fig. 5. Distribution of regression coefficients (B) between log(10) SARS-CoV-2 concentrations and log(10) COVID-19 cases in the monitored population over time (n = 38).

period. These findings suggest that SARS-CoV-2 measured at wastewater sites is strongly associated with levels of COVID-19 cases in the population across a variety of catchments.

The regressions undertaken in this paper, enable a quantification of the relationship between COVID-19 cases and SARS-CoV-2 concentrations in wastewater. However, to understand how useful this would be it is important to consider between and within catchment uncertainty in the relationship between COVID-19 cases and SARS-CoV-2 concentrations in wastewater (detailed analysis in Supplementary Material) and what this means in terms of estimated case numbers.

Assessment of between catchment uncertainty (illustrated in Supplementary Material Fig. 3), indicates that the relationship between log(10) SARS-CoV-2 concentrations in wastewater and log(10) COVID-19 cases varies across catchments. We have calculated a conservative quantification of this between catchment uncertainty by estimating the number of cases in each of the 452 catchments based upon the median SARS-CoV-2 concentrations in wastewater. This was done separately for SNS and STW catchments. For SNS and STW catchments we then report the ratio of the upper quartile to the lower quartile of estimated cases. For STW this ratio is over 6 and for SNS this ratio around 4. This indicates that between catchments, for a given SARS-CoV-2 concentration in wastewater, COVID-19 case estimates vary substantially. Factors influencing the regression coefficients were explored giving some indication of the source of this between catchment variability. The multiple regression results indicated that for both STW and SNS in larger catchments each unit of SARS-CoV-2 in wastewater led to proportionally greater numbers of COVID-19 cases. In both STW and SNS in catchments with an increasing proportion of grab samples each unit of SARS-CoV-2 in wastewater led to proportionally lower numbers of COVID-19 cases. Finally, for STW with an increasing proportion of white British in the population grab each unit of SARS-CoV-2 in wastewater led to proportionally lower number of COVID-19 cases. Taken together these findings suggest prediction of COVID-19 cases based on the concentration of SARS-CoV-2 in wastewater over multiple catchments is complex. This suggests that studies aiming to estimate case numbers based on concentrations in wastewater may be more effective on a catchment-by-catchment basis. This concurs with studies elsewhere that have struggled to predict cases from concentration across a range of sites (Kisand et al., 2023; Fitzgerald et al., 2021).

Within catchments there is also uncertainty. For each catchment the estimate of the relationship between log(10) SARS-CoV-2 concentrations in wastewater and log(10) COVID-19 cases was estimated with error. A conservative quantification of this uncertainty is to use the residuals from regression models to estimate, for each of the 452 catchments, the ratio of the upper quartile of estimated cases to the lower quartile of estimated cases. For STW this ratio is over 5 and for SNS this ratio is over 3. Again, this indicates that within catchments COVID-19 case estimates vary substantially based upon uncertainty in the regression models.

Our analysis of correlation coefficients, focusing on 38 STW sites with data throughout the study, demonstrated a shift over time. There was a small decrease in median correlation values between Time 1 (July 2020 to January 2021; Wild Type into Alpha) and Time 2 (Jan to July 2021; Alpha into Delta) from strong (0.80) to moderate (0.58) correlation. During Time 3 (July to December 2021; Delta into Omicron), weak almost negligible correlation (0.05) existed. During Time 3 the Delta variant was dominant and COVID-19 cases remained relatively high, increasing substantially towards the end of the study period when Omicron became dominant (UKHSA, 2023). However, from the start of this period SARS-CoV-2 concentrations in wastewater decreased. This shift in correlations was also mirrored in the regression coefficients. Times 1 and 2 showed similar coefficients and similarity between wastewater catchments, while the range of regression coefficients between wastewater catchments became highly variable in Time 3 During this period decreasing levels of SARS-COV-2 concentration in wastewater were observed alongside increasing COVID-19 cases in the population, which has been noted elsewhere (UKHSA, 2022b).

One explanation for the changing relationship between SARS-COV-2 concentrations in wastewater and COVID-19 cases in the population, could be the efficacy of the qRT-PCT assay used to detect SARS-COV-2 in wastewater. If the assay had reduced effectiveness in detecting the circulating variant, then levels of SARS-COV-2 in wastewater would appear lower. However, there is little evidence for this, efficacy was a challenge with Omicron rather than Delta which was dominant during Time 3. Alternatively, during Time 3 COVID-19 cases may have been shedding less SARS-CoV-2 to wastewater. During Time 3 there was a shift in COVID-19 cases towards younger people (UKHSA, 2023). It has been suggested that COVID-19 infection is often mild in children (Nathanielsz et al., 2023), however whether this results in lower viral loads and shedding is inconclusive (Puhach et al., 2023). It seems unlikely this would have driven such a large change in the relationship. From the summer of 2021 there was a relaxation of movement restrictions which may have impacted the relationship between testing location and location of shedding. People who have been vaccinated shed the virus for a shorter time (Garcia-Knight et al., 2022), and by the start of Time 3, the initial vaccination campaign of two doses had resulted in the vaccination of almost all those who eventually accepted vaccine (ONS, 2023b). During this period immunity to COVID-19 is likely to have been varying due to the protective effect of vaccine against infection declining over time (Puhach et al., 2023), especially following the introduction of the AstraZeneca vaccine (a viral vector vaccine, widely distributed in England during 2021) (UKHSA, 2022a). In some groups immunity would have been increasing due to the roll out of the third vaccine from late September. Potentially varying levels of immunity could lead to variable SARS-CoV-2 shedding rates, despite relatively high case numbers. A combination of these factors may explain the poorer correlations and more variable regression coefficients between COVID-19 cases in the community and SARS-CoV-2 concentrations in wastewater during Time 3.

There are limitations to this research. Firstly, the registered address of the COVID-19 case may differ from the location where faecal material entered the wastewater catchment. This is particularly an issue for areas with high numbers of mobile populations (e.g. university students) who may not have been staying at their registered postcode. This was more likely in the early dates of this study as in 2021 this was changed to the address provided where the test was taken. Just over a third of wastewater samples had SARS-CoV-2 present at levels below the LOD. Although this introduces uncertainty, we overcame this issue using censored regression techniques. Future analysis could apply smoothing techniques to infer wastewater concentrations for censored data (Lewis-Borrell et al., 2023). It could be argued that variation in SARS-CoV-2 concentration in wastewater could be due to differences in in individual shedding rates between catchments (Cavany et al., 2022; Challenger et al., 2022), but most of our understanding of variability in shedding rates of SARS-CoV-2 viral loads come from nasopharyngeal swabs and these concentrations do not correlate well with virus shed in faeces (Daou et al., 2022). Also, on a catchment scale any differences would likely be averaged out between catchments (Wade et al., 2022).

The use of different laboratories to analyse the wastewater data and the ongoing development of analytical methods in this evolving field could have brought uncertainty into the findings. However, the consistency of our findings across all sites suggests that this was not a substantive issue. While studies have suggested that the use of consistent methods and a single laboratory is the ideal (Davis et al., 2023), the use of different methods and different laboratories to analyse wastewater can result in consistent results with a high degree of reproducibility (Pecson et al., 2021; Chik et al., 2021). The predominant source of our case data was derived from PCR results and a variety of surveillance factors may affect these numbers (Mercer and Salit, 2021). The use of self-administered Lateral Flow Tests (LFT)s became increasingly common as the pandemic progressed. Studies have shown that the positive predictive value of LFT is lower during periods of low prevalence, but are effective when prevalence is high (Hogg et al., 2023). Therefore, during periods of particularly low or high prevalence during our study, we acknowledge that case numbers derived from self-reported LFT results could be variable.

During our study COVID-19 was highly prevalent and it would be interesting to contrast results during periods of low virus circulation. Two sites (one STW and one SNS) had negative correlation and regression coefficients indicating that as concentrations rose, cases fell. No geographical, socio-demographic or sampling explanation was found to explain why these sites had unusual values. They were not at the extremes of any measures examined and they were not located near each other. The reasons for these anomalous values are unclear.

Despite all the known variability and limitations, this work aimed to explore whether wastewater SARS-CoV-2 concentrations, determined through rapidly developed and evolving processes as a response to the pandemic, correlated to known human cases identified through rapidly set up, scaled and adapted national testing within the same catchment areas over time.

Our findings support the suggestion that WBS is an effective method of determining the dynamics of COVID-19 in the population (Carrillo-Reyes et al., 2021; Wade et al., 2022). It is unlikely there will be another situation soon that will provide the level of community population-based testing for a pathogen that the COVID-19 pandemic afforded. WBS is still undertaken at a small scale in England (University of Bath, 2024), and knowing WBS can be rapidly deployed to effectively survey the situation in the population indicates it could be used more widely to determine pathogen presence in the population.

5. Conclusions

Wastewater monitoring was rapidly introduced at scale to England during COVID-19. This enabled us to undertake one of the largest studies on the associations between SARS-CoV-2 concentrations in wastewater and COVID-19 in the population. Our analysis included nearly 95,000 wastewater samples, collected from 452 wastewater sites (259 STW and 193 SNS) across 18 months, and incorporating 65 % of the English population. These were matched to 6 million confirmed COVID-19 cases. During this period laboratory methods were continuously assessed and improved and case ascertainment is likely to have varied. Combined with the highly diverse nature of our catchments it is notable that our findings consistently indicate that for both STW and SNS at the wastewater catchment level, SARS-COV-2 concentration in wastewater correlates well with COVID-19 cases in the surrounding area. The median correlation coefficients for STW and SNS were just under what would be regarded as strong and were remarkably similar irrespective of the characteristics of the wastewater catchments. The precise relationship between SARS-CoV-2 concentrations in wastewater and COVID-19 cases in the population was very uncertain suggesting that predicting COVID-19 cases based upon WBS is less reliable and may be more appropriate at the scale of individual wastewater catchment. Changes in the correlation and regression coefficients over time were observed, with the relationships weaker and more varied in the final six months (15th July 2021 to 19th December 2021) compared to earlier periods. Reasons for this are unknown but could reflect the vaccination status of the population studied.

CRediT authorship contribution statement

Natalia R. Jones: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Richard Elson:** Writing – review & editing, Methodology, Formal analysis. **Matthew J. Wade:** Writing – review & editing, Data curation. **Shannon McIntyre-Nolan:** Writing – review & editing, Data curation. **Andrew Woods:** Writing – review & editing, Data curation. **James Lewis:** Writing – review & editing, Data curation. **Diane Hatziioanou:** Writing – review & editing, Data curation. **Roberto Vivancos:** Writing – review & editing, Data curation. **Paul R. Hunter:** Writing – review & editing. **Iain R. Lake:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2025.178455.

Data availability

The UKHSA welcomes applications from organisations looking to use these data, and all applications will be rigorously reviewed using an objective, standards-based process. Potential applicants should contact DataAccess@ukhsa.gov.uk.

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