Current environmental monitoring cannot constrain the effect of vaccines on SARS-CoV-2 transmission: Report for SAGE 08/04/2021

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SAGE Discussion

1. *With consideration to the results presented in this paper, are there any alternative applications for wastewater-based epidemiology in monitoring the effectiveness of COVID-19 vaccines?*

2. *This paper presents a model developed to predict COVID-19 case rates based on SARS-CoV-2 RNA concentrations observed in wastewater. Are there additional use cases that could be pursued as a priority, as we continue to develop wastewater as a quantitative indicator of COVID-19 cases in the community?*

Abstract

This paper presents summary statistics of wastewater data and a Bayesian hierarchical log-linear regression model developed to predict weekly COVID-19 case rates (NHS Pillar 1 and 2) based on wastewater surveillance data. Outputs are analysed to investigate whether the AstraZeneca and Pfizer/BioNTech vaccines inhibit SARS-CoV-2 infection and transmission in addition to preventing symptomatic disease. No significant deviation was observed between reported case rates and SARS-CoV-2 RNA concentrations in wastewater. However, three confounding factors have been identified that limit the interpretation of this analysis: changes in NPI, the emergence of B.1.1.7, and a change in laboratory methodology. Therefore, the results presented in this paper cannot be considered evidence of COVID-19 vaccines preventing transmission of SARS-CoV-2. While the insight provided by wastewater in interrogating the impact of vaccines on SARS-CoV-2 transmission is limited, the Environmental Monitoring for Health protection programme has, and will continue to, provide surveillance and outbreak support in the COVID-19 response.

Introduction

Routine analysis of wastewater (WW) samples for infectious disease surveillance beyond the monitoring of waterborne pathogens is a relatively new scientific field (Daughton, 2001). It has gained significant attention recently, due to its demonstrated utility in monitoring the COVID-19 pandemic (Medema *et al.*, 2020). Led by the Joint Biosecurity Centre and Defra Group under the Environmental Monitoring for Health Protection programme (EMHP), wastewater-based epidemiology (WBE) for SARS-CoV-2 has been operational in England since July 2020 (as previously reported to SAGE; Wade *et al*., 2020). WW samples collected from sewage treatment works (STW), in-network sites, and near-to-source infrastructure sites currently provide coverage of over two-thirds of the English population. Through the provision of insight into community transmission, wastewater monitoring has aided national and local responses to the pandemic. For example, a companion paper for this meeting (Brown *et al*., 2021) discuss the value added through WBE in detecting the emergence and spread of SARS-CoV-2 Variants of Concern (VOC) and Variants Under Investigation (VUI). A previous report to SAGE (Wade *et al.,* 2020) presents the currently operational use cases.

The UK COVID-19 vaccines delivery plan commenced in December 2020 and is expected to transform the epidemiological landscape of COVID-19. To date, more than 30 million individuals in the UK, constituting over 58.7% of the adult population, have received their first dose of either the AstraZeneca (ChAdOx1) or Pfizer/BioNTech (BNT162b2) vaccine (GOV.UK , 2021). As of 15th February 2021, every individual belonging to the top four priority groups defined by the Joint Committee on Vaccination and Immunisation (JCVI, 2020), has been invited to receive their first dose of either vaccine (PHE, 2021). Nevertheless, evidence of disparities in vaccine uptake between deprivation deciles is becoming apparent, and greater levels of vaccine hesitancy have been noted, for example in some ethnic minority groups (The OpenSAFELY Collaborative *et al.*, 2021; ONS, 2021).

The evidence base for ChAdOx1 and BNT162b2 protecting against SARS-CoV-2-related morbidity and mortality is growing (Hall, 2021; Bernal *et al.*, 2021). However, questions remain on whether vaccine efficacy is mediated only by symptom prevention, or if ChAdOx1 and BNT162b2 also prevent infection and infectiousness. The latter is particularly important in the context of predicting the likelihood of further epidemic waves and instituting non-pharmaceutical interventions (NPIs) to limit their impact. It was hypothesised that WBE may be able to address this question and inform the deployment of targeted health messaging and resources to encourage vaccine uptake in areas of persistent transmission as it offers a representative signal of infection amongst the population resident in the catchment area of each treatment works. To assess the suitability of wastewater data to constrain the impact of vaccination on infection and infectivity, we sought to establish whether the relationship between case rates and SARS-CoV-2 concentrations in wastewater changed in response to vaccination uptake.

We developed predictive models for case rates based on wastewater surveillance data, as discussed in the Methods, to study the relationship and identify any potential change. While the approach remains relevant and may eventually prove useful, as demonstrated in the

Results, it was not possible to constrain the mediator of vaccine efficacy because of confounding factors. These are the third national lockdown, a change in laboratory methodology, and the emergence of new variants of SARS-CoV-2 that may be associated with different faecal viral loads. These limitations are addressed in more depth in the Discussion. The inability to adequately assess infectivity in vaccinated populations does not undermine the utility of WBE as a useful and cost-effective quantitative surveillance tool.

Results

The median SARS-CoV-2 gene copy concentration per reported case per 100,000 people across each of the 44 treatment sites was considered, as shown in *Figure 1* (a). This summary statistic is a useful tool for an initial investigation into the impact of ChAdOx1 and BNT162b2 on infection and transmission. For example, if vaccines only prevent symptoms but not infection or transmission, the reported number of cases would be expected to fall whereas wastewater SARS-CoV-2 RNA concentrations would remain high. Consequently, the ratio would increase. As shown in *Figure 1* (a), no significant change was observed in response to the vaccine rollout in England. However, a contemporaneous rise of infections due to the B.1.1.7 variant, a change in lab methodology, and introduction of the third national lockdown confound this relationship.

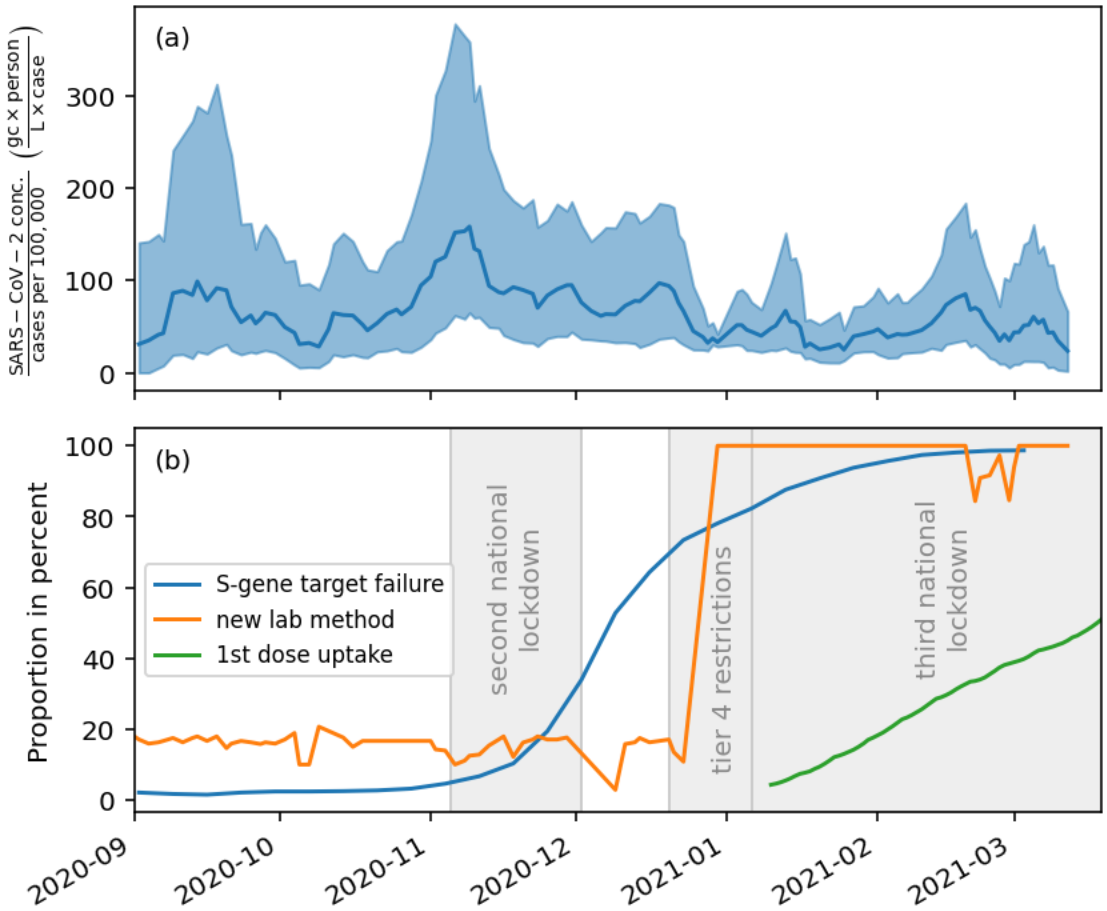

Figure 1: Panel (a) shows the seven-day rolling average of the median SARS-CoV-2 concentration per cases per 100,000 people (solid blue line) together with the interquartile range (shaded region). No significant change is observed in response to the vaccine rollout shown as the uptake of the 1st vaccination dose amongst the adult population (green) in panel (b). The proportion of PCR tests with S-gene target failure (indicative of the B.1.1.7 variant) is shown in blue in panel (b), and the proportion of wastewater samples processed using an improved laboratory method in orange.

In order to further investigate the impact of the UK vaccination programme on SARS-CoV-2 transmission, a Bayesian hierarchical log-linear regression model (Carlin *et al.*, 2003) was developed to predict weekly case rates, i.e. weekly rolling case numbers per 100,000 individuals from NHS Test & Trace Pillar 1 and 2, falling within the catchment areas of 44 wastewater treatment sites. These sites have been monitored since July 2020 as part of EMHP's national wastewater surveillance programme. The model allows for parameters to vary between different sites and pools information across sites where data are not sufficient to constrain site-level parameters. Predictions are based on physiochemical and biological properties of each collected wastewater sample (such as the concentration of SARS-CoV-2 gene copies or the concentration of ammoniacal nitrogen). The median absolute deviation of predictions on the logarithmic scale (base 10) for a held-out test set is 0.22, i.e. half of the predictions are within 0.22 orders of magnitude of the true case rates.

The model not only predicts the rate of cases per 100,000, but it also estimates prediction errors. It thus facilitates a shift from merely observing correlations between case rates and the concentration of SARS-CoV-2 RNA in wastewater samples to using wastewater-based surveillance as a quantitative tool. For example, Figure 2 shows predictions of case rates for the Beckton treatment works in London together with well-calibrated bounds on the prediction errors (see Methods for details).

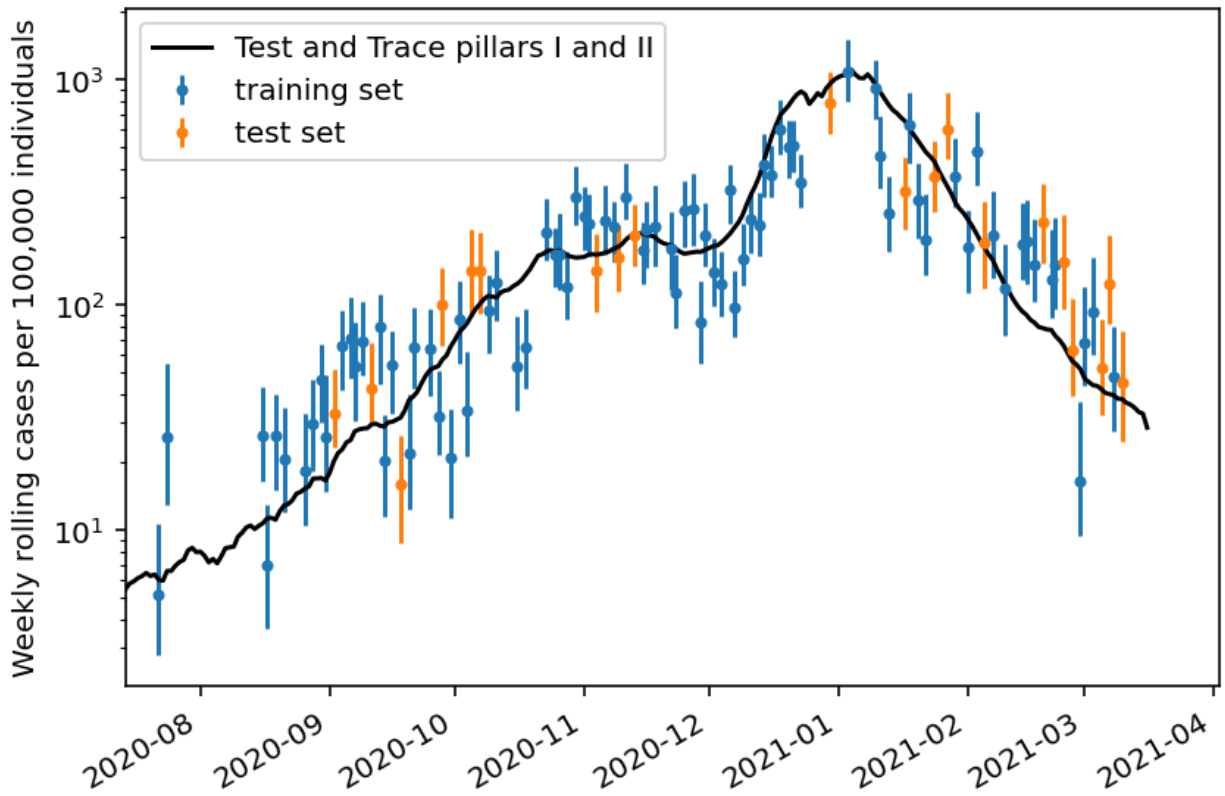

Figure 2: Wastewater-based predictions of weekly case rates track data from NHS Test and Trace pillars 1 and 2 well for both the training and test sets. Predictions are shown for the Beckton sewage treatment works in London, and they are based on a single sample collected on the same date as Test and Trace specimen were obtained. Error bars represent the interquartile range of the posterior predictive distribution of the model.

Wastewater-based predictions are consistent with the decline in cases starting in early January. However, it was not possible to identify the extent to which ChAdOx1 and BNT162b2 prevents onwards transmission of SARS-CoV-2 given the available data because there are three confounding factors that are considered in more depth in the Discussion. Briefly, the vaccination programme was rolled out at the same time as the proportion of cases associated with the B.1.1.7 variant increased, improved laboratory methods for wastewater samples were adopted, and NPIs were updated (Figure 1 (b)). Furthermore, it is currently not known whether and to what extent vaccination affects faecal RNA shedding.

The model, described in the Methods, comprises regression coefficients for the predictions as well as the prediction errors. As shown in panel (a) of Figure 3, the concentration of SARS-CoV-2 gene copies is strongly predictive of weekly case rates, and gene copy concentrations being below the limit of detection implies a lower case rate (compared with typical SARS-CoV-2 RNA concentration values). The concentration of ammoniacal nitrogen (a metabolite of urea) and orthophosphates (from human waste

as well as industrial and agricultural contributions) are indicative of how dilute a given sample is (Been, *et al.*, 2014). Lower concentrations imply more dilution because the total load is expected to be approximately constant over time for each site. This intuition is reflected in the negative regression coefficients for ammoniacal nitrogen and orthophosphate concentrations, and the model has learnt to account for variable dilution: all else being equal, decreases in marker concentration should lead to larger predicted case rates. Finally, an indicator variable was used to control for the effect of different laboratory methods for concentrating SARS-CoV-2 RNA. The virus RNA concentration method is a critical step in the RT-qPCR procedure for lab-based virus quantification. Ammonium sulphate (AS) precipitation (as opposed to polyethylene glycol (PEG) precipitation) was, all else being equal, found to be associated with lower case rates. This implies that AS precipitation is more effective at recovering the RNA signal from wastewater samples, however parallel data in laboratory settings are insufficient to confirm this assessment. Regardless, AS precipitation presents a significant processing time benefit over PEG precipitation and has been adopted by laboratory partners in the EMHP programme to minimise time to reporting.

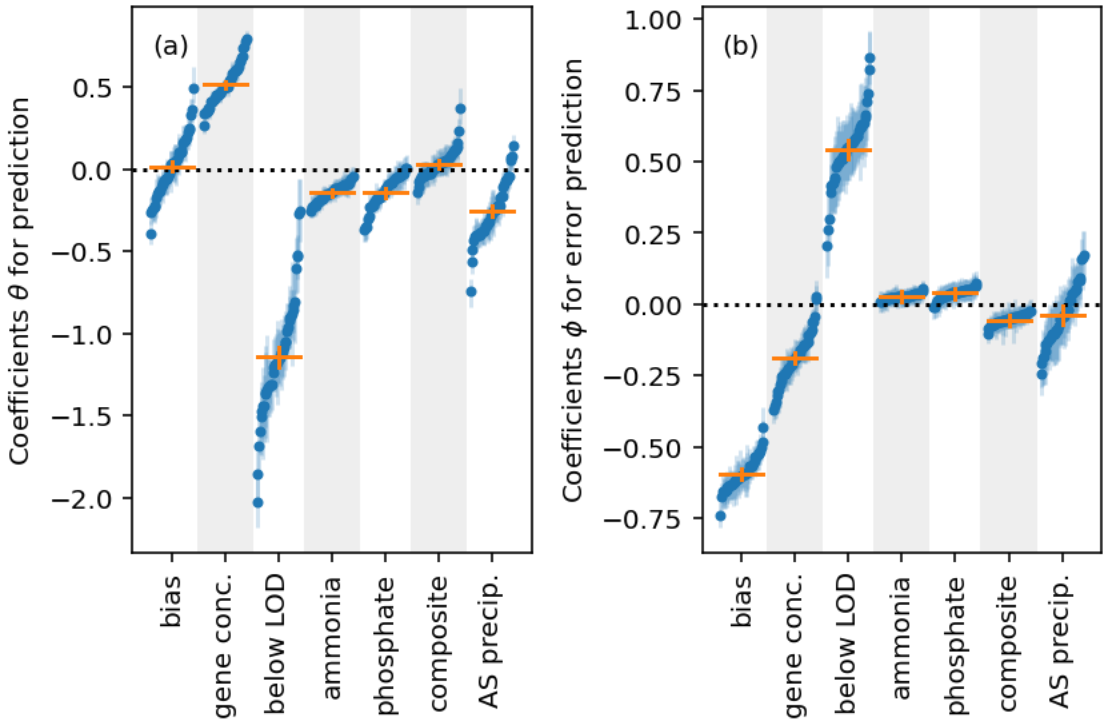

Figure 3: Model parameters capture the relationship between weekly case rates and data from wastewater samples. Regression coefficients for predicting weekly case rates are shown in panel (a). Positive coefficients imply that an increase in the associated covariate results in an increased case rate prediction. Each blue marker corresponds to one of 44 treatment sites that are part of the national programme with the posterior interquartile range (IQR) shown as error bars. The orange horizontal and vertical lines show the posterior mean and IQR of typical coefficients inferred across sites. Coefficients for estimating prediction errors are shown in panel (b), and positive coefficients imply that an increase in the associated covariate results in an increased prediction error.

The regression coefficients for estimating the prediction errors on the log scale are shown in panel (b) of Figure 3. Increases in SARS-CoV-2 RNA concentration are associated with smaller prediction errors.

Similarly, prediction errors are large when the concentration is below the limit of detection. The use of composite samples (as opposed to grab samples) and use of AS precipitation are both associated with marginal decreases in prediction error on average, although this is not observed not for all sites.

Discussion

Environmental monitoring is based on detecting SARS-CoV-2 viral RNA in wastewater that is shed in the faeces and other bodily fluids of infected individuals. It was therefore hypothesised that the effect of vaccination on SARS-CoV-2 transmission could be explored by analysing the deviation between SARS-CoV-2 RNA concentrations in wastewater samples and case rates following the large-scale rollout of ChAdOx1 and BNT162b2. While the rich data collected by EMHP has facilitated the development of well-calibrated predictive models for weekly case rates based on wastewater surveillance data (as presented in the

Results), no significant deviation between case rates and wastewater surveillance data was observed since the beginning of the vaccination programme. Even if deviations were observed, it would not be possible to establish the impact of vaccinations on transmission because of three confounding factors.

First, as shown in *Figure 1* (b), the proportion of cases associated with the B.1.1.7 variant changed rapidly over the same period as the vaccine rollout programme. Analysis of the median cycle threshold values of respiratory samples that resulted in failure to detect the S-gene target (SGTF) indicates viral loads are higher in individuals infected with the B.1.1.7 variant compared to previously dominant strains in the UK (Kidd *et al*., 2021). Any change in relationship between case rates and wastewater signals could thus be due to changing faecal RNA shedding rates if the pattern in respiratory samples was reproduced in faecal samples. Faecal shedding data for infections due to the B.1.1.7 variant are not currently available.

Second, the method used to concentrate RNA extracted from wastewater samples was changed during the early stages of the vaccine rollout. PEG precipitation was replaced by ASe precipitation, decreasing incubation time from 18 hours to one hour. However, this change in methodology further complicates identifying a change in relationship between case rates and wastewater data due to vaccine uptake because estimated SARS-CoV-2 concentrations pre and post method change are not necessarily directly comparable.

Finally, the third national lockdown was introduced in England on 5th January 2021. Marked declines in community prevalence have since been observed in REACT data (Riley *et al.*, 2021), and similar trends noted in positive cases detected through Pillar 1 and 2 symptomatic testing. The vast majority of vaccine uptake has occurred since lockdown was enforced, as shown in *Figure 1* (b). Whilst not infeasible in principle, any additional effect of vaccinations on transmission would have to be assessed against a background of strongly suppressed transmission due to non-pharmaceutical interventions.

Given currently available data, we are therefore not able to determine through the association between SARS-CoV-2 RNA concentrations in wastewater and case rates whether declines in concentration described in the

Results are solely attributable to NPIs reducing transmission and therefore case rates and faecal shedding, or if ChAdOx1 and BNT162b2 also prevent transmission of SARS-CoV-2.

Applications and future directions

While the current predictive ability of wastewater-based surveillance is promising, expanding these models to include temporal structure and use information from multiple samples (such as distributed lag models) is likely to increase the predictive performance. Explicitly modelling prediction errors will continue to highlight areas of improvement for the EMHP wastewater surveillance programme. For example, laboratory methods are being considered to lower the limit of quantification and detection and new approaches to sample collection are being explored to reduce noise. Hierarchical modelling approaches will facilitate integrating new sites into the national surveillance programme to expand the population coverage of WBE and aid monitoring of public health beyond COVID-19. The value of mechanistic (or process-based) modelling in supporting the study and management of environment-related health issues is increasingly recognised (Beltrame *et al*., 2021), and opportunities for using mechanistic modelling in wastewater-based epidemiology are also being explored. Mechanistic modelling could complement statistical models by providing a rationale for the nature of the relation between prevalence and concentrations of the virus in wastewater. It could also help explain the noise in the data over time, as well as variability between sites. Identifying where the data conflict with process-based estimates could highlight opportunities for improving the collection and processing of data. Comparing process-based estimates of prevalence from wastewater data under different assumptions (vaccination/no vaccination, different NPIs) could be an alternative way of exploring the influence of these interventions.

While WBE has been of limited use in assessing the impact of vaccines on SARS-CoV-2 transmission, the EMHP programme has provided insight into areas of stubborn transmission, increasing prevalence of SARS-CoV-2, community transmission of VOC/VUIs, and infection trends in settings including prisons and schools. These insights have aided local and national teams in planning and responding to COVID-19, and we will continue to expand on the operational use cases detailed in Wade *et al*., 2020 and Brown *et al*., 2021 as WBE analytical capabilities and capacity develop further.

Methods

Data collection and processing

Operational and technical details, including laboratory analyses undertaken by the Environment Agency and Bangor University, are described in full in Wade *et al*. (2020) and Jones *et al*. (2020). Briefly, samples were collected from each of 44 wastewater treatment works four times a week from July 2020 to March 2021 and transported to laboratories on ice. The concentration of SARS-CoV-2 RNA in each of 5,132 samples was estimated using RT-qPCR using the N1 gene target developed by the CDC (Lu, et al., 2020). Where the concentration was below the limit of detection (LOD) of the assay (12.6% of samples), the concentration was imputed using the site-level median over the entire observation period. To account for the LOD, a binary feature was added to the data that indicates whether the viral RNA concentration was detectable. Samples that did not provide any information on SARS-CoV-2 concentration (20.7%), i.e. samples that were neither labelled as having a concentration below the LOQ or offered a quantitative value, were removed. The concentration of ammoniacal nitrogen and orthophosphates were also determined by colorimetric assays. Missing values for these auxiliary data were median imputed by site (1.2% for ammoniacal nitrogen, 2.3% for orthophosphates). Metadata for each sample, such as the laboratory method used for processing the sample and whether the sample was a grab or composite sample, were also available. Concentrations were log-transformed and all continuous features were

standardised to have zero mean and unit variance. Binary features were mean-subtracted but left unscaled (Gelman, 2007).

The number of Pillar 1 and 2 cases reported by NHS Test and Trace at the level of lower-layer super output areas (LSOAs) were projected onto catchment areas of wastewater treatment works and aggregated by specimen date. Case numbers were divided by the population resident in each catchment to obtain case rates and joined with wastewater data by date. Dates on which case rates were zero were excluded from the analysis because this small subset (0.6% of the data) cannot be captured by a log-linear model.

Model

No two sewerage systems are the same, and a model that pools information globally cannot account for the idiosyncrasies of different systems (Banks, et al., 2017). However, the relationship between case rates and wastewater-based surveillance data is expected to follow broadly similar patterns. For example, the correlation between case rates and SARS-CoV-2 concentration is likely positive across sites, but the specific dependence may vary. Thus, hierarchical models that can pool information across sites where data are insufficient to constrain site-level parameters was developed (Carlin, Stern, Rubin, & Gelman, 2003). At the same time, parameters can vary between sites where the data provide sufficient evidence.

In particular, let X_{tij} denote the value of feature j for sewage treatment works i at time t and let y_{ti} denote the rolling weekly case rate for the population in the catchment area of treatment works i at time t. Then

$$\log y_{ti} \sim \text{Normal}\left(\eta_{ti}, \sigma_{ti}^2\right),$$

where η_{ti} and σ_{ti}^2 are the prediction and prediction variance for y_{ti}, respectively. They are given by

$$\eta_{ti} = \sum_{j=1}^{k} \theta_{ij} X_{tij} \qquad \text{and} \qquad \log \sigma_{ti} = \sum_{j=1}^{k} \phi_{ij} X_{tij},$$

and the parameters θ_{ij} encode the impact feature j has on predictions for site i. Similarly, the coefficients ϕ_{ij} encode the effect of feature j on the noise profile for site i. The precision of predictions is thus allowed to vary from sample to sample and between sites.

The parameters share a hierarchical prior across sites such that

$$\theta_{ij} \sim \text{Normal}\left(\mu_j, \lambda_j^2\right) \qquad \text{and} \qquad \phi_{ij} \sim \text{Normal}\left(\nu_j, \tau_j^2\right),$$

where μ and ν capture the mean value of the parameters θ and ϕ at the population level, respectively, and they are given improper flat priors. The parameters λ_j^2 and τ_j^2 capture the variability between sites and are given half-Cauchy priors.

Inference and validation

Training and test sets were obtained by performing an 80-20 split of the dataset stratified by treatment site. Splitting the dataset temporally (i.e. pre and post vaccination) was also considered to identify any change in relationship between wastewater and case data in response to vaccinations. However,

contemporaneous changes in the proportion of cases associated with the B.1.1.7 variant, NPIs, and laboratory methods make it impossible to attribute any change to vaccinations (see *Figure 1* (b)). The model was implemented in Stan (Stan Development Team, 2021), and it was fitted to the training set by drawing samples from the posterior distribution. Inferred parameters are summarised in Figure 3, and predictions are compared with the true values in the left column of Figure 4, showing that the model is able to make accurate predictions. The median absolute deviation on the log scale (base 10) for the training and test sets is 0.21 and 0.22, respectively.

To determine whether the estimated prediction errors are well calibrated, replicates of the weekly case rates $y^{(\mathrm{rep})}$ were generated from the posterior predictive distribution (PPD) of the model, and the α-PPD interval (i.e. the interval that contains a fraction α of the mass of the PPD) was evaluated. If the model is well calibrated, the coverage probability $p^{(\mathrm{train})}(\alpha)$ of the α-PPD interval (i.e. the fraction of true values $y^{(\mathrm{train})}$ that are contained within the interval) is equal to α (Carlin, Stern, Rubin, & Gelman, 2003). Indeed, $p^{(\mathrm{train})}(\alpha) \approx \alpha$ for all values of α, as shown in panel (b) of Figure 4. Predictions of the weekly case rates $y^{(\mathrm{pred})}$ were also generated for the held-out test set, and the coverage probability $p^{(\mathrm{test})}(\alpha)$ was evaluated. As shown in panel (d), $p^{(\mathrm{test})}(\alpha) \approx \alpha$. The model is not only able to make accurate predictions of weekly case rates out of sample, but it can also estimate its own prediction errors.

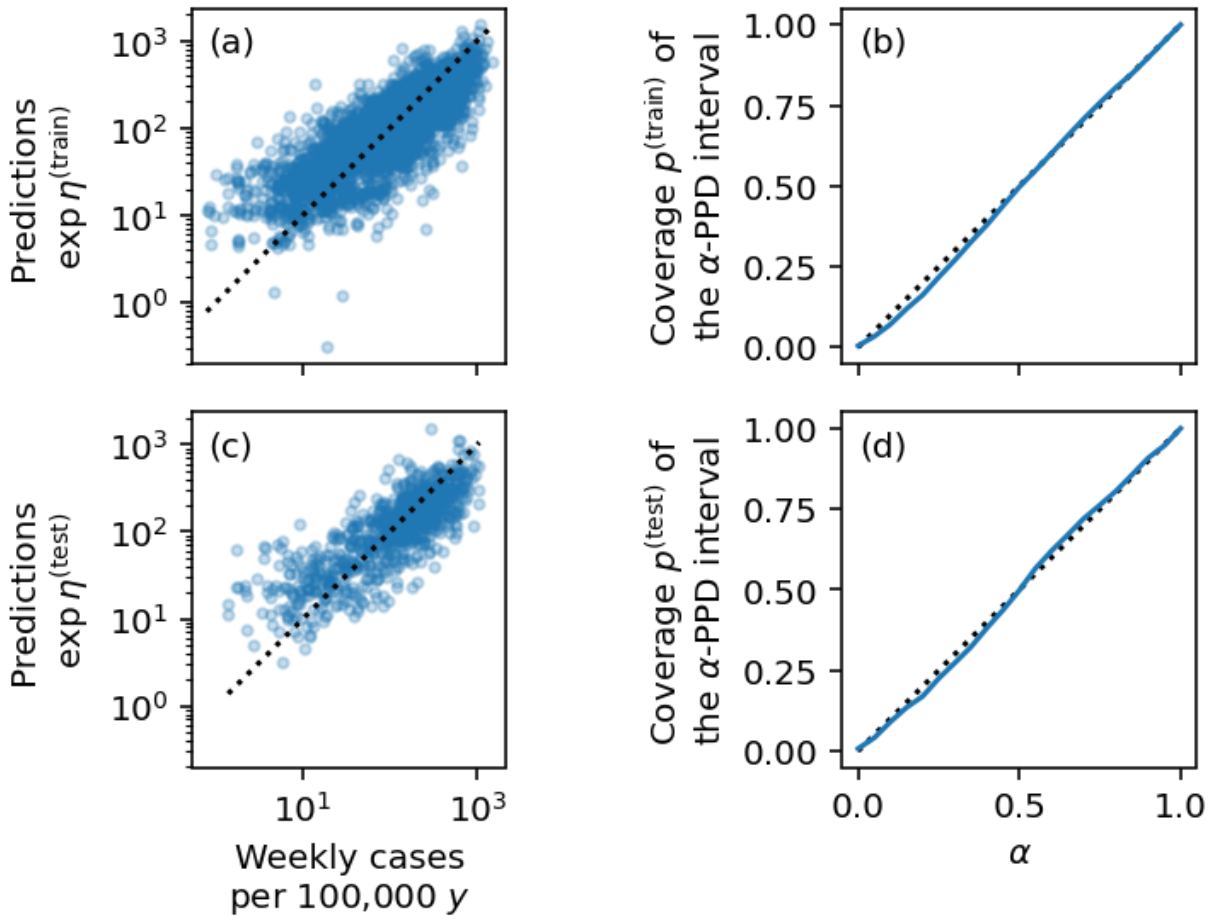

Figure 4: The model can make accurate predictions for both the training and test set and is well calibrated. Panels (a) and (c) show predictions of the model exp η *against the true weekly case rates y for the training*

and test sets, respectively. Panel (b) shows the coverage probability $p^{(\text{train})}(\alpha)$ of the interval containing a fraction α of the mass of the posterior predictive distribution (PPD). Similarly, panel (c) shows the coverage probability $p^{(test)}(\alpha)$ of the α-PPD interval for held-out data.

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