

# Supplemental Material:

## Estimating Rates of Change to Interpret Quantitative Wastewater Surveillance of Disease Trends

David A. Holcomb<sup>a,b</sup>, Ariel Christensen<sup>a,c</sup>, Kelly Hoffman<sup>b</sup>, Allison Lee<sup>b</sup>, A. Denene Blackwood<sup>d</sup>, Thomas Clerkin<sup>d</sup>, Javier Gallard-Góngora<sup>d</sup>, Angela Harris<sup>e</sup>, Nadine Kotlarz<sup>f</sup>, Helena Mitasova<sup>g,h</sup>, Stacie Reckling<sup>c,g</sup>, Francis L. de los Reyes III<sup>e</sup>, Jill R. Stewart<sup>b</sup>, Virginia T. Guidry<sup>c</sup>, Rachel T. Noble<sup>b,d</sup>, Marc L. Serre<sup>b</sup>, Tanya P. Garcia<sup>i,†</sup>, Lawrence S. Engel<sup>a,†,\*</sup>

<sup>a</sup> Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

<sup>b</sup> Department of Environmental Sciences and Engineering, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

<sup>c</sup> Occupational & Environmental Epidemiology Branch, Division of Public Health, North Carolina Department of Health and Human Services, Raleigh, NC, USA

<sup>d</sup> Institute of Marine Sciences, Department of Earth, Marine and Environmental Sciences, University of North Carolina at Chapel Hill, Morehead City, NC, USA

<sup>e</sup> Department of Civil, Construction and Environmental Engineering, North Carolina State University, Raleigh, NC, USA

<sup>f</sup> Department of Biological Sciences, North Carolina State University, Raleigh, NC, USA

<sup>g</sup> Center for Geospatial Analytics, North Carolina State University, Raleigh, NC, USA

<sup>h</sup> Department of Marine, Earth and Atmospheric Sciences, North Carolina State University, Raleigh, NC, USA

<sup>i</sup> Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

† TG and LE are co-senior authors

This supplement contains 48 pages, 3 tables, and 31 figures.

## Table of Contents

Table of Contents .....	2
S1 Gaussian Process Derivatives .....	3
S1.1 Jointly Sampling a Gaussian Process and its Derivative .....	3
S1.2 Predicting Derivatives of a Gaussian Process.....	4
S2 Squared Exponential Kernel Function .....	7
S3 Smoothing with Generalized Additive Models.....	8
S4 Simulating Reported Case Counts .....	9
S5 Indirect Simulation of Wastewater Viral Loads .....	11
S6 Analysis Code .....	14
S7 Simulation Study Rate of Change Estimates .....	15
S8 Estimation Performance by Simulation Scenario .....	16
S9 Plateau Classification by Simulation Scenario .....	18
S10 North Carolina Sewersheds Characteristics .....	19
S11 Relative Performance of Estimation Methods in NC Sewersheds.....	20
S12 Trend Classifications in NC Sewersheds.....	21
S13 Sewersheds-Specific Rate of Change Estimates .....	22
S14 Supplementary References.....	47

## S1 Gaussian Process Derivatives

### S1.1 Jointly Sampling a Gaussian Process and its Derivative

A Gaussian process (GP) represents a distribution over all the possible smooth functions of a continuous domain (e.g., time) and is defined by its covariance function that relates any pair of locations on that domain, with any finite set of observations following a multivariate normal distribution.<sup>1-3</sup> Sampling a GP at a finite set of locations  $\mathbf{z}$  provides the outputs  $\mathbf{x}$  of a single smooth function  $f(\mathbf{z})$  evaluated at each of those points, with the function behavior determined by the covariance kernel function  $k(z_i, z_j | \boldsymbol{\theta})$  with hyperparameters  $\boldsymbol{\theta}$  for each pair of locations  $z_i, z_j$ :

$$\begin{aligned} \mathbf{x} &= f(\mathbf{z}) \\ f(\mathbf{z}) &\sim \mathcal{GP}\left(k(z_i, z_j | \boldsymbol{\theta})\right) \end{aligned} \quad (\text{S1})$$

The first derivative  $f'(\mathbf{z})$  of the smooth function is also distributed as a GP with covariance kernel function  $k'(z_i, z_j | \boldsymbol{\theta})$ , the derivative of the original covariance function with respect to the locations  $z_i$  and  $z_j$ .<sup>4-6</sup>

$$\begin{aligned} f'(\mathbf{z}) &\sim \mathcal{GP}\left(k'(z_i, z_j | \boldsymbol{\theta})\right) \\ k'(z_i, z_j | \boldsymbol{\theta}) &= \frac{\partial}{\partial z_i \partial z_j} k(z_i, z_j | \boldsymbol{\theta}) \end{aligned} \quad (\text{S2})$$

This feature allows values of both the smooth function  $f(\mathbf{z})$  and its derivative  $f'(\mathbf{z})$  to be obtained simultaneously for all locations  $\mathbf{z}$  by sampling jointly from the GP and its derivative, enabling us to simulate both a smooth trend and its instantaneous rate of change at any finite set of time points. Designating the original covariance kernel function  $k_{00}(z_i, z_j) = k(z_i, z_j | \boldsymbol{\theta})$  and its derivative at the same locations  $k_{11}(z_i, z_j) = k'(z_i, z_j | \boldsymbol{\theta})$ , the covariance between the trend value  $x_i$  at location  $z_i$  and the derivative value  $x'_j$  at location  $z_j$  is given by

$$k_{01}(z_i, z_j) = k_{10}(z_j, z_i) = \frac{\partial}{\partial z_j} k(z_i, z_j | \boldsymbol{\theta}) \quad (\text{S3})$$

We can then sample  $\mathbf{x}^{all} = \begin{bmatrix} \mathbf{x} \\ \mathbf{x}' \end{bmatrix}$  at positions  $\mathbf{z}^{all} = \begin{bmatrix} \mathbf{z}^x \\ \mathbf{z}^{x'} \end{bmatrix}$  by defining an indicator vector

$\mathbf{d}^{all} = \begin{bmatrix} \mathbf{d}^x = 0 \\ \mathbf{d}^{x'} = 1 \end{bmatrix}$ , calculating the joint covariance matrix  $\Sigma^{all}$  as

$$\Sigma_{ij}^{all} = \begin{cases} k_{00}(z_i, z_j), & d_i = 0, d_j = 0 \quad (\text{both normal observations}) \\ k_{01}(z_i, z_j), & d_i = 0, d_j = 1 \quad (\text{one normal, one derivative}) \\ k_{10}(z_i, z_j), & d_i = 1, d_j = 0 \quad (\text{one derivative, one normal}) \\ k_{11}(z_i, z_j), & d_i = 1, d_j = 1 \quad (\text{both derivatives}) \end{cases} \quad (\text{S4})$$

and sampling  $\mathbf{x}^{all}$  from a multivariate normal distribution as  $\begin{bmatrix} \mathbf{x} \\ \mathbf{x}' \end{bmatrix} \sim \text{MVN}(0, \Sigma^{all})$ .<sup>4,5</sup>

### S1.2 Predicting Derivatives of a Gaussian Process

An alternative to jointly sampling from a GP and its derivative is to sample only from the GP and predict the derivative observations  $\mathbf{x}'$  conditional on the sampled observations  $\mathbf{x}$  at the same locations  $\mathbf{z}$ . To predict unobserved GP values  $\mathbf{x}_{pred} = f(\mathbf{z}_{pred})$  using observed GP values  $\mathbf{x}_{obs} = f(\mathbf{z}_{obs})$ , the conditional probability distribution is also multivariate normal:

$$\mathbf{x}_{pred} | \mathbf{x}_{obs} \sim \text{MVN}(\mathbf{m}, \mathbf{K}) \quad (\text{S5})$$

The prediction mean vector  $\mathbf{m}$  has an analytical solution given by

$$\mathbf{m} = \mu_{pred} + (\Sigma_{01})^T (\Sigma_{00})^{-1} (\mathbf{x}_{obs} - \mu_{obs}) \quad (\text{S6})$$

where  $\mu_{pred}$  and  $\mu_{obs}$  are the means for the prediction and observation locations, respectively (which for simplicity we usually set to zero beforehand by mean-centering),  $\Sigma_{01}$  is the covariance between all observed and predicted points given by the kernel function  $k(z_{obs}, z_{pred})$ , and  $\Sigma_{00}$  is the covariance matrix between observed locations given by the kernel function  $k(z_{obs}, z_{obs})$ . Likewise, the prediction covariance matrix  $\mathbf{K}$  is obtained analytically as

$$\mathbf{K} = \Sigma_{11} - (\Sigma_{01})^T (\Sigma_{00})^{-1} \Sigma_{01} \quad (\text{S7})$$

for the covariance matrix  $\Sigma_{11}$  between all prediction locations produced by the kernel function  $k(z_{pred}, z_{pred})$ .<sup>3,7</sup>

Predicted derivative values  $\mathbf{x}'$  conditional on the observations  $\mathbf{x}$  at the same locations  $\mathbf{z}' = \mathbf{z}$  can be obtained as the conditional prediction mean vector  $\mathbf{m}$ :

$$\begin{aligned}
 \mathbf{x}' &= \mathbf{m} \\
 &= \mu' + (\Sigma_{01})^T (\Sigma_{00})^{-1} (\mathbf{x} - \mu) \\
 &= 0 + (\Sigma_{01})^T (\Sigma_{00})^{-1} (\mathbf{x} - 0) \\
 &= (\Sigma_{01})^T (\Sigma_{00})^{-1} (\mathbf{x}) \\
 &= (k_{01}(\mathbf{z}^x, \mathbf{z}^{x'}))^T (k_{00}(\mathbf{z}^x, \mathbf{z}^x))^{-1} (\mathbf{x})
 \end{aligned} \tag{S8}$$

where  $k_{00}$  is the covariance kernel function defined previously for use with pairs of normal GP observations and  $k_{01}$  is the kernel function used for one normal observation and one derivative observation. As the derivative predictions are all for the same locations as the observations, there is no prediction error and it is unnecessary to evaluate  $\mathbf{K}$ . To illustrate, Figure S1 presents sampled GP observations and both the jointly-sampled derivative and the predicted derivative using a squared exponential kernel covariance function with  $\alpha = 1$  and  $\rho = 1$ . We can visually confirm that both approaches yield equivalent values of the GP derivative and that the derivative crosses zero wherever the GP has a local minimum or maximum.

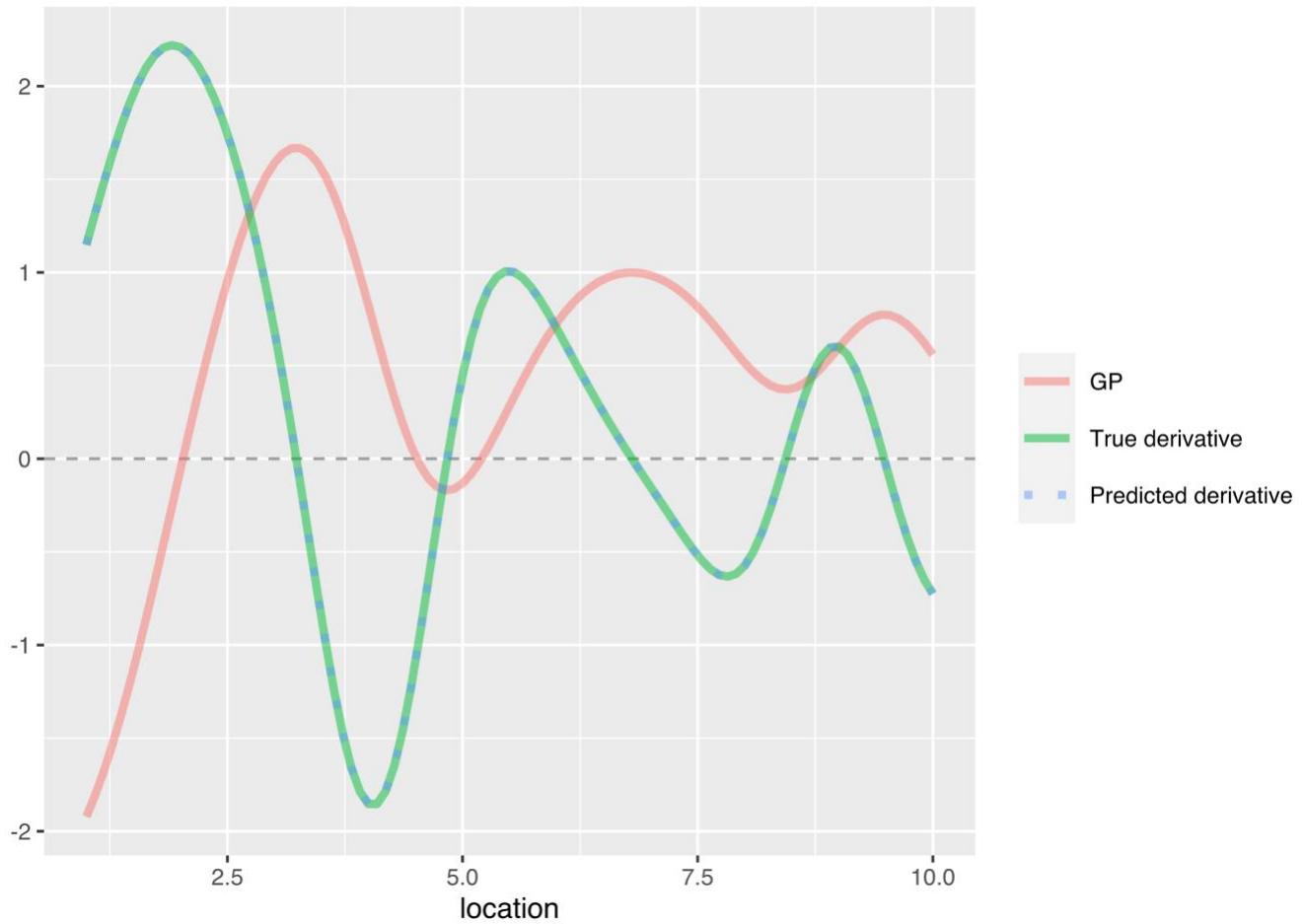


Figure S1. Comparison of jointly sampled (green solid line) and predicted (blue dotted line) derivatives of a sampled GP (red solid line)

## S2 Squared Exponential Kernel Function

The squared exponential kernel covariance function is defined as

$$k_{00}^{sqe}(z_i, z_j | \alpha, \rho) = \alpha^2 \exp\left(-\frac{1}{2} \left(\frac{z_i - z_j}{\rho}\right)^2\right) \quad (\text{S9})$$

where  $\alpha$  is the marginal standard deviation, a scale hyperparameter that controls the magnitude of the covariance.<sup>5</sup> For the special case  $z_i = z_j$ , the exponential term reduces to  $\exp(0) = 1$  and  $k(z_i, z_i) = \alpha^2$ . The rate at which correlation decays with increasing distance between locations  $z_i$  and  $z_j$  is controlled by the range hyperparameter  $\rho$ , which corresponds to the distance between  $z_i$  and  $z_j$  for which the maximum covariance  $\alpha^2$  has been reduced by approximately 40%. The derivative of the squared exponential kernel function  $k_{11}^{sqe}(z_i, z_j | \alpha, \rho)$  for the covariance between derivative observations at locations  $z_i$  and  $z_j$  is given by:

$$k_{11}^{sqe} = \frac{\partial}{\partial z_i \partial z_j} k_{00}^{sqe}(z_i, z_j | \alpha, \rho) = \frac{\alpha^2}{\rho^4} \left(\rho^2 - (z_i - z_j)^2\right) \exp\left(-\frac{1}{2} \left(\frac{z_i - z_j}{\rho}\right)^2\right) \quad (\text{S10})$$

and the kernel function  $k_{01}^{sqe}(z_i, z_j | \alpha, \rho)$  for an observation at  $z_i$  and a derivative observation at  $z_j$  is:

$$k_{01}^{sqe} = \frac{\partial}{\partial z_j} k_{00}^{sqe}(z_i, z_j | \alpha, \rho) = \frac{\alpha^2}{\rho^2} (z_i - z_j) \exp\left(-\frac{1}{2} \left(\frac{z_i - z_j}{\rho}\right)^2\right) \quad (\text{S11})$$

### S3 Smoothing with Generalized Additive Models

Smooth functions are commonly estimated using regression splines, in which polynomial regressions are fit to contiguous subsets of the observed data and constrained to have equal values, first derivatives, and second derivatives at the bounds of each subset (“knot”) to produce a piecewise, smooth function over the temporal range of the data.<sup>8–11</sup> Introducing additional knots to subset the data more finely allows the resulting function to more closely trace the observed data, while fewer knots induce a smoother curve. Rather than manually specifying the number and locations of knots, an excess of knots may be supplied and smoothness instead induced by introducing a penalty based on the second derivative of the spline (which increases as the smoothness decreases) and an additional smoothness parameter that adjusts the strength of the penalty. Penalized splines are readily implemented as smooth predictor terms in a generalized additive model (GAM), a flexible extension of the generalized linear model that has previously demonstrated good performance estimating smooth trends in wastewater SARS-CoV-2 viral loads, among other times series applications.<sup>8,10,12</sup> The first derivative of each smooth predictor in a fitted GAM can be estimated for any point within the range of the data due to the continuous support of GAM-estimated smooths.<sup>1,13</sup> GAMs also provide a smoothness selection-corrected Bayesian covariance matrix to account for the uncertainty introduced by estimating the spline smoothness parameter, allowing confidence intervals (CIs) to be constructed for both the estimated smooth term and any estimated derivatives.<sup>1,10</sup>

## S4 Simulating Reported Case Counts

The multivariate imputation approach also required simulated daily case counts that shared an underlying trend with the simulated viral loads. While viral loads were simulated on a logarithmic scale with a mean of zero for simplicity (analogous to analyzing mean-centered data), case counts were simulated on the arithmetic scale by exponentiating the log scale-sampled trend, for which an additive mean on the log scale is meaningful. To simulate integer-valued case counts, we specified a sewershed population of  $P = 200,000$  individuals and a long-run mean infection rate  $\bar{\lambda} = 0.0005$  (5 cases per 10,000 population). Furthermore, we assumed only 60% of infections were reported ( $F_{report} = 0.6$ ) with a lag of three days after infection ( $l_{report} = 3$ ). These conditions yielded a mean of 100 daily new infections, which were log-transformed and added to sampled trend value  $x_t$  to obtain the infection log-incidence rate  $x_t^{incident}$  on study day  $t$  before scaling by the reporting proportion to generate the reported log-incidence rate  $x_t^{report}$ . Independent Gaussian errors  $\epsilon_t^{case}$  (distinct from the wastewater errors  $\epsilon_t^{ww}$  but sharing the same standard deviation  $\sigma$ ) were sampled and added to the reported log-incidence rate to obtain an over-dispersed case log-incidence rate  $\ln(\lambda_t)$ . Case counts were generated by sampling from a Poisson distribution with rate  $\lambda_t$  and assigning the count sampled for day  $t$  as the observed count three days hence to account for the specified reporting lag  $l_{report}$ :

$$\begin{aligned}
 y_{t+l_{report}}^{case,obs} &= y_t^{case} \\
 y_t^{case} &\sim \text{Poisson}(\lambda_t) \\
 \ln(\lambda_t) &= x_t^{report} + \epsilon_t^{case}, \quad \epsilon_t^{case} \sim N(0, \sigma^2) \\
 x_t^{report} &= x_t^{incident} + \ln(F_{report}) \\
 x_t^{incident} &= \mu^{incident} + x_t \\
 \mu^{incident} &= \ln(\bar{\lambda}P)
 \end{aligned} \tag{S12}$$

for the observed case count  $y_{t+l_{report}}^{case,obs}$  on day  $t + l_{report}$ . Examples of simulated cases for each of the scenarios are displayed in Figure S2, where under-reporting of cases relative to the trend is apparent.

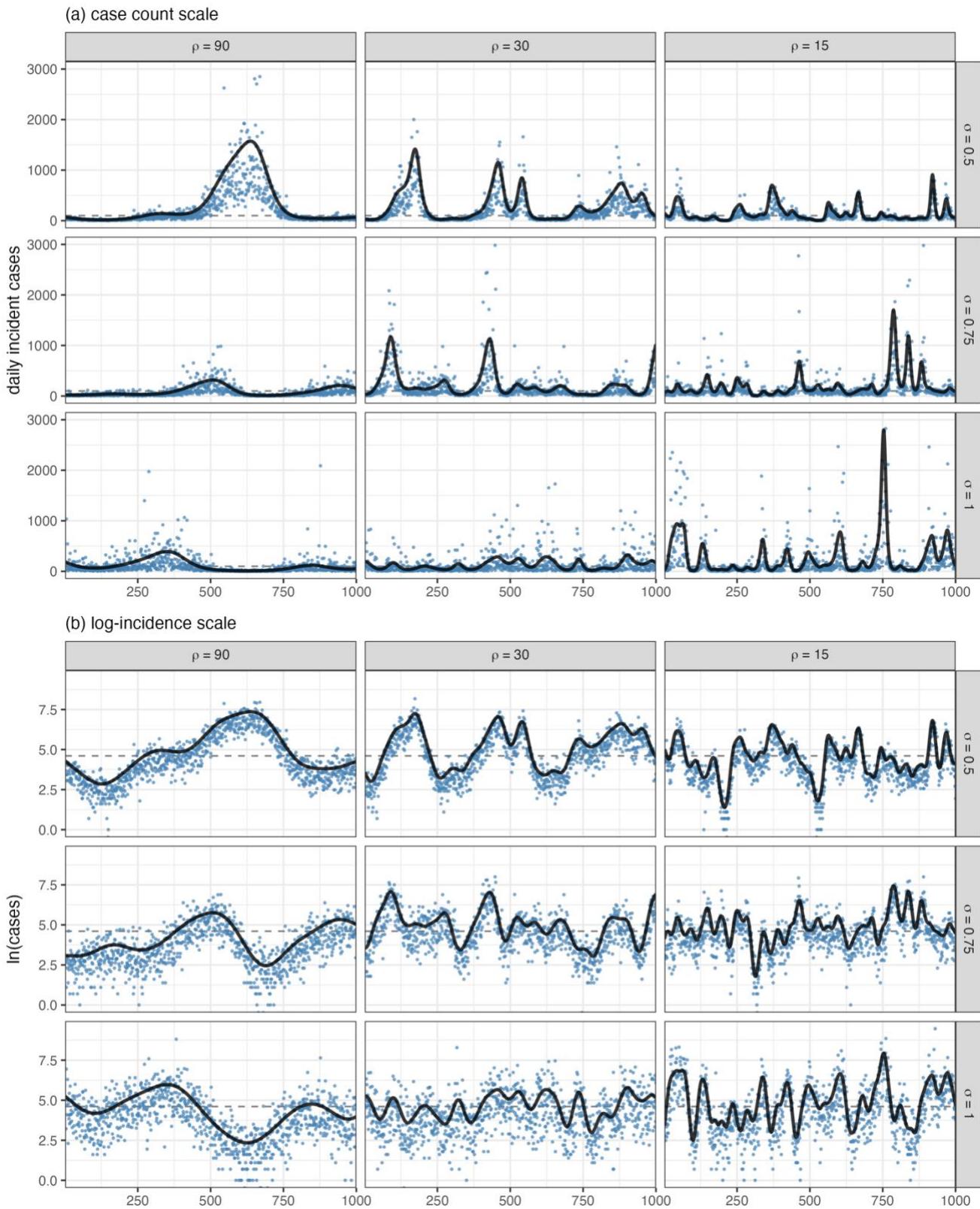


Figure S2. Synthetic reported cases simulated across nine scenarios presented on the (a) raw data scale of daily case counts and (b) natural log-incidence scale, on which the smooth trend was sampled

## S5 Indirect Simulation of Wastewater Viral Loads

When simulating wastewater measurements, the Gaussian process-sampled trend  $x_t$  corresponds to log-viral load—related to the prevalence of actively shedding infections<sup>14</sup>—but represent log-incident infections when simulating case counts. To address this inconsistency, we also simulated wastewater viral loads using an indirect approach similar to the case simulation approach based on a consistent log-incident infections definition of the sampled GP trend. To translate incident infections into viral loads, the same daily log-incident infections  $x_t^{incident}$  on day  $t$  used in the case simulations were summed over an assumed 14-day average fecal shedding duration of the  $D_{shed}$  days preceding each time  $t$ , yielding the infection log-prevalence  $x_t^{prev}$ . We specified that 80% of infections shed virus in feces ( $F_{shed} = 0.8$ ) and that the average shedding infection contributed  $L = 10^5$  viral gene copies/day to the wastewater viral load (that is, the virus per infection arriving at the sampling location after any dilution and loss during transport),<sup>15</sup> with a one-day lag  $l_{shed}$  from infection onset for an indirect  $\log_{10}$  wastewater viral load  $y_{t+l_{shed}}^{indirect,obs}$  observed on day  $t = l_{shed}$ :

$$\begin{aligned}
 y_{t+l_{shed}}^{indirect,obs} &= y_t^{indirect} \\
 y_t^{indirect} &= \log_{10}(x_t^{ww}) + \epsilon_t^{ww} \\
 x_t^{ww} &= x_t^{prev} \times F_{shed} \times L \\
 x_t^{prev} &= \sum_{d=0}^{D_{shed}} \exp(x_{t-d}^{incident}) \\
 x_t^{incident} &= \mu^{incident} + x_t \\
 \mu^{incident} &= \ln(\bar{\lambda}P)
 \end{aligned} \tag{S13}$$

Because the GP-sampled trend  $x_t$  corresponds to incident infections for the indirectly simulated wastewater observations, the true trend in wastewater viral loads must also be calculated from the cumulative infections over the specified shedding duration and its first derivative is no longer known exactly. Compared with directly simulated viral load trends and observations, the scale of the indirect wastewater trends is notably compressed, relative to the variance of the synthetic observations, while maintaining the same shape (Figure S3).

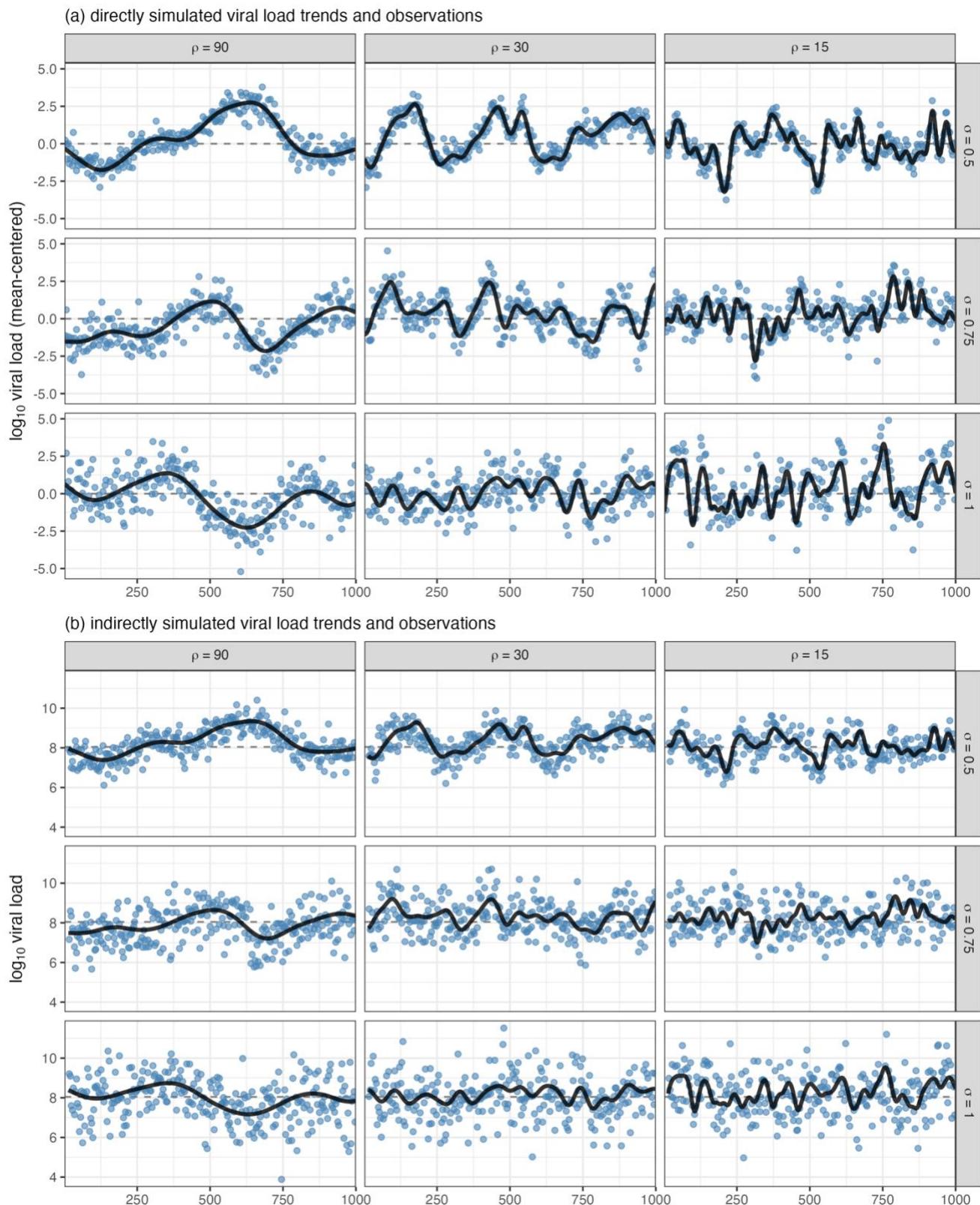


Figure S3. Comparison of wastewater trends and observations across nine simulation scenarios for (a) viral loads simulated directly from the GP-sampled trend and (b) indirectly simulated viral loads where the GP-sampled trend corresponds to log-incident infections

As our primary aim was to evaluate methods for estimating rates of change in wastewater analyte trends—*independent* of population infection metrics—and we simulated cases only to implement an estimation approach drawn from the literature for comparison purposes,<sup>16</sup> we used synthetic wastewater observations simulated directly from the sampled trend for all analyses. Indirectly simulated wastewater observations may be more appropriate for evaluating methods intended to relate wastewater measurements with population-level metrics, for example estimating the prevalence of infections or illicit drug use in a sewershed population, where the relationship between cases and wastewater is crucial and the true rate of change is of secondary interest. Such applications would likely benefit from careful consideration of the simulation parameter values assumed (e.g., global mean incidence rate, shedding proportion and duration, reporting fraction and lag, etc.) to ensure realistic relationships between wastewater- and population-based synthetic data.<sup>15</sup>

## S6 Analysis Code

The R code to conduct both the simulation analysis and to produce rate of change estimates for the real-world NC wastewater SARS-CoV-2 viral load monitoring data is available at <https://doi.org/10.17605/OSF.IO/BPGN4>. The custom functions written to implement the analysis are provided both in an R script (“roc\_functions.R”) that can be sourced for direct use and described in detail in an HTML report (“roc\_notebook.html”). Additionally, a compressed R project folder (“wastewaterRateOfChange.zip”) is provided that contains all the data and code necessary to reproduce the HTML report. To do so, download the compressed file to a computer with recent versions (e.g., released in mid-2022 or later) of the RStudio integrated development environment (IDE) and the R platform installed and unzip it. Within the unzipped directory, open the “wastewaterRateOfChange.Rproj” file to launch the project in a new R session in RStudio. Use the “Open” dialogue within RStudio to navigate to the “roc\_notebook.qmd” Quarto markdown file in the “script” subdirectory. Install any missing packages as prompted; the code can now be run interactively through the .qmd file or in its entirety using the “render” functionality in RStudio to reproduce the HTML report.

## S7 Simulation Study Rate of Change Estimates

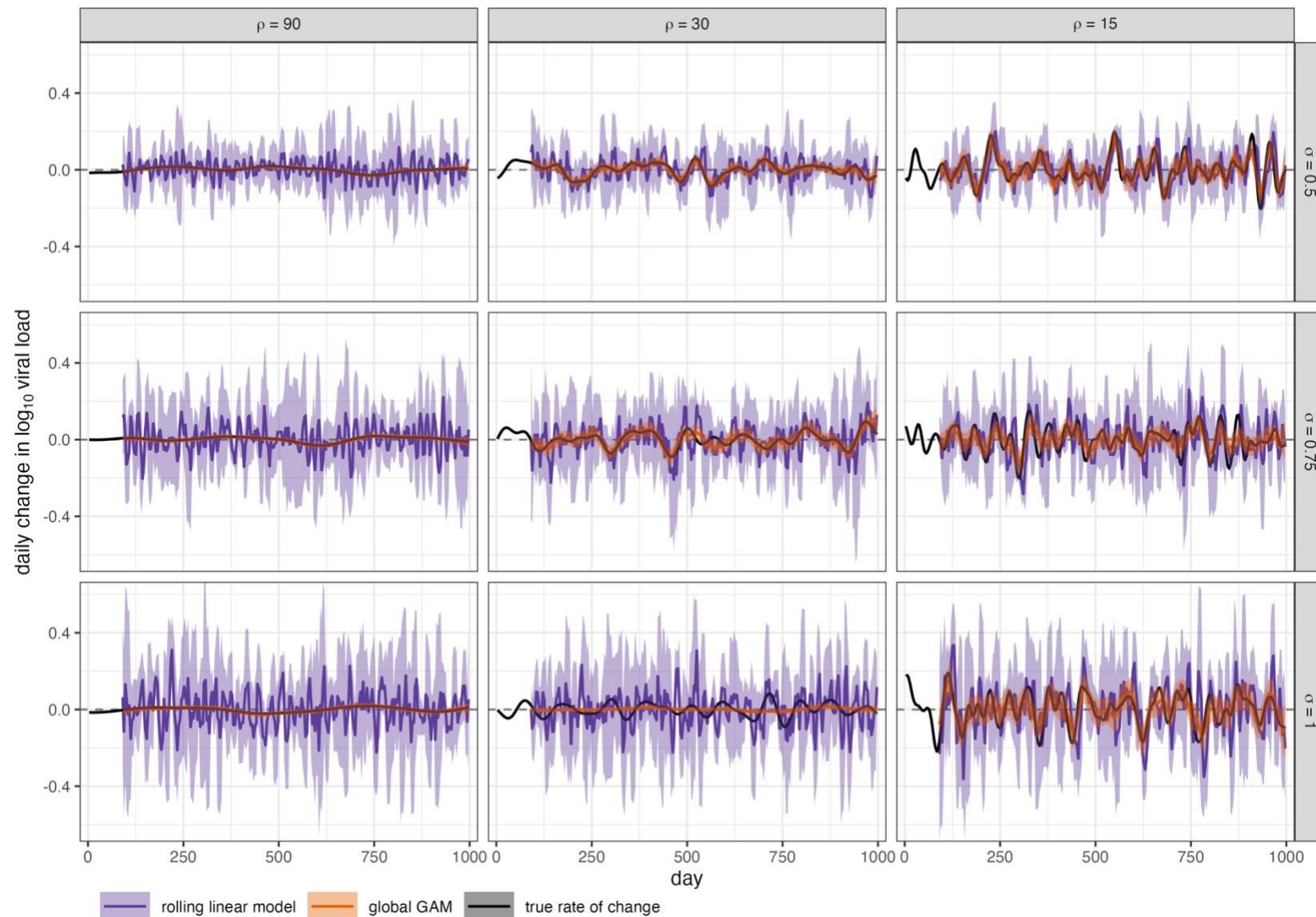


Figure S4. Mean and 95% CI estimated rates of change by the rolling linear model (purple) and GAM fit to the full dataset (orange) compared with the true first derivative of the viral load trend (black) for illustrative realizations of the nine simulation scenarios

## S8 Estimation Performance by Simulation Scenario

Table S1. Median (2.5th – 97.5th percentiles) of estimation performance across nine simulation scenarios with differing degrees of smoothness ( $\rho$ ) and observation noise ( $\sigma$ )

$\rho$	$\sigma$	Method	RMSE [ $\Delta \log_{10}$ gc/day]	Mean 95% CI Width [ $\Delta \log_{10}$ gc/day]	95% CI Coverage [%]	Sensitivity [%]	Specificity [%]	AUC [%]
<i>Scenario 1: high smoothness, low noise</i>								
0.5	90	rolling linear model	0.04 (0.04, 0.05)	0.27 (0.24, 0.29)	95 (92, 98)	58 (51, 65)	58 (51, 65)	60 (55, 67)
		multivariate imputation	0.02 (0.02, 0.03)	0.07 (0.06, 0.08)	88 (81, 93)	64 (54, 74)	63 (54, 74)	69 (59, 79)
		univariate imputation	0.01 (0.01, 0.02)	0.04 (0.03, 0.04)	78 (66, 89)	70 (59, 82)	70 (59, 82)	78 (67, 87)
		rolling GAM	0.01 (0.01, 0.01)	0.04 (0.02, 0.05)	92 (72, 100)	76 (56, 89)	75 (54, 88)	82 (62, 93)
		global GAM	0.00 (0.00, 0.00)	0.02 (0.01, 0.02)	100 (95, 100)	93 (76, 100)	92 (75, 100)	98 (91, 100)
<i>Scenario 2: high smoothness, moderate noise</i>								
0.75	90	rolling linear model	0.07 (0.06, 0.08)	0.40 (0.36, 0.44)	95 (92, 98)	55 (49, 62)	55 (49, 62)	57 (52, 63)
		multivariate imputation	0.03 (0.03, 0.04)	0.11 (0.10, 0.12)	88 (82, 93)	59 (51, 69)	59 (51, 70)	63 (55, 73)
		univariate imputation	0.02 (0.02, 0.02)	0.06 (0.05, 0.06)	84 (72, 93)	66 (55, 78)	65 (55, 75)	72 (61, 82)
		rolling GAM	0.01 (0.01, 0.01)	0.04 (0.02, 0.06)	90 (64, 99)	71 (44, 87)	71 (44, 87)	76 (51, 90)
		global GAM	0.00 (0.00, 0.01)	0.02 (0.01, 0.03)	100 (83, 100)	91 (69, 100)	91 (67, 100)	98 (85, 100)
<i>Scenario 3: high smoothness, high noise</i>								
1	90	rolling linear model	0.09 (0.08, 0.10)	0.53 (0.47, 0.59)	95 (92, 98)	54 (48, 61)	54 (48, 60)	55 (50, 61)
		multivariate imputation	0.04 (0.04, 0.05)	0.14 (0.13, 0.16)	88 (83, 93)	57 (48, 66)	57 (50, 65)	60 (53, 68)
		univariate imputation	0.02 (0.02, 0.03)	0.07 (0.07, 0.08)	87 (76, 95)	63 (52, 73)	62 (53, 73)	68 (57, 78)
		rolling GAM	0.01 (0.01, 0.02)	0.04 (0.02, 0.07)	88 (57, 99)	67 (36, 86)	67 (36, 85)	70 (41, 87)
		global GAM	0.00 (0.00, 0.01)	0.02 (0.01, 0.03)	100 (62, 100)	89 (60, 100)	90 (60, 100)	96 (77, 100)
<i>Scenario 4: moderate smoothness, low noise</i>								
0.5	30	rolling linear model	0.05 (0.04, 0.05)	0.26 (0.24, 0.29)	95 (91, 97)	68 (60, 77)	68 (60, 76)	74 (66, 82)
		multivariate imputation	0.03 (0.03, 0.04)	0.08 (0.07, 0.08)	74 (64, 82)	71 (62, 79)	71 (62, 80)	78 (69, 85)
		univariate imputation	0.03 (0.02, 0.03)	0.04 (0.03, 0.04)	49 (39, 60)	75 (66, 84)	75 (65, 84)	81 (73, 88)
		rolling GAM	0.03 (0.02, 0.04)	0.12 (0.08, 0.15)	93 (78, 99)	71 (58, 80)	71 (58, 81)	78 (65, 86)
		global GAM	0.01 (0.01, 0.01)	0.06 (0.04, 0.07)	100 (93, 100)	90 (80, 97)	90 (79, 97)	97 (92, 99)
<i>Scenario 5: moderate smoothness, moderate noise</i>								
0.75	rolling linear model	0.07 (0.06, 0.08)	0.40 (0.36, 0.44)	95 (91, 97)	63 (55, 71)	63 (56, 70)	67 (60, 75)	

$\rho$	$\sigma$	Method	RMSE [ $\Delta \log_{10} \text{gc/day}$ ]	Mean 95% CI Width [ $\Delta \log_{10} \text{gc/day}$ ]	95% CI Coverage [%]	Sensitivity [%]	Specificity [%]	AUC [%]
0.5	0.05	multivariate imputation	0.04 (0.03, 0.05)	0.11 (0.10, 0.12)	81 (73, 88)	67 (57, 75)	67 (57, 75)	73 (63, 81)
		univariate imputation	0.03 (0.02, 0.04)	0.05 (0.05, 0.06)	60 (48, 72)	72 (61, 81)	71 (62, 80)	78 (69, 86)
		rolling GAM	0.03 (0.03, 0.04)	0.12 (0.07, 0.18)	90 (65, 99)	65 (48, 77)	65 (47, 76)	70 (51, 82)
		global GAM	0.01 (0.01, 0.02)	0.06 (0.04, 0.08)	98 (78, 100)	86 (72, 95)	86 (72, 95)	94 (85, 98)
	Scenario 6: moderate smoothness, high noise							
	1	rolling linear model	0.09 (0.08, 0.10)	0.53 (0.48, 0.59)	95 (92, 98)	60 (53, 68)	60 (53, 67)	64 (56, 71)
		multivariate imputation	0.05 (0.04, 0.06)	0.15 (0.13, 0.16)	84 (77, 90)	64 (55, 73)	64 (55, 72)	69 (60, 78)
		univariate imputation	0.03 (0.03, 0.04)	0.07 (0.07, 0.08)	68 (55, 79)	69 (59, 78)	69 (59, 78)	75 (65, 83)
		rolling GAM	0.04 (0.03, 0.05)	0.13 (0.06, 0.20)	88 (50, 98)	60 (40, 73)	60 (41, 72)	63 (42, 77)
		global GAM	0.02 (0.01, 0.02)	0.07 (0.03, 0.09)	94 (48, 100)	83 (64, 94)	83 (65, 94)	91 (76, 98)
	Scenario 7: low smoothness, low noise							
0.75	0.5	rolling linear model	0.07 (0.06, 0.08)	0.27 (0.24, 0.30)	89 (83, 93)	70 (62, 77)	69 (62, 77)	76 (69, 82)
		multivariate imputation	0.08 (0.06, 0.09)	0.09 (0.08, 0.10)	42 (34, 52)	58 (49, 67)	58 (49, 68)	61 (52, 70)
		univariate imputation	0.07 (0.05, 0.08)	0.04 (0.04, 0.04)	23 (17, 30)	65 (57, 73)	65 (57, 73)	68 (61, 76)
		rolling GAM	0.06 (0.05, 0.08)	0.21 (0.15, 0.26)	89 (75, 95)	68 (57, 77)	68 (57, 77)	75 (63, 83)
		global GAM	0.03 (0.02, 0.03)	0.11 (0.08, 0.12)	95 (82, 99)	87 (78, 94)	87 (78, 94)	95 (89, 98)
	Scenario 8: low smoothness, moderate noise							
15	0.75	rolling linear model	0.08 (0.07, 0.09)	0.40 (0.36, 0.44)	92 (88, 96)	66 (58, 73)	66 (58, 74)	71 (64, 78)
		multivariate imputation	0.08 (0.06, 0.09)	0.12 (0.11, 0.13)	53 (44, 63)	58 (49, 67)	58 (50, 66)	61 (52, 70)
		univariate imputation	0.07 (0.05, 0.08)	0.06 (0.05, 0.06)	31 (23, 41)	64 (55, 73)	64 (55, 73)	68 (59, 76)
		rolling GAM	0.07 (0.06, 0.09)	0.22 (0.12, 0.30)	85 (58, 95)	60 (44, 71)	60 (44, 71)	64 (45, 77)
		global GAM	0.04 (0.03, 0.05)	0.11 (0.07, 0.14)	87 (57, 98)	82 (68, 91)	82 (69, 91)	90 (79, 96)
	Scenario 9: low smoothness, high noise							
1	1	rolling linear model	0.10 (0.09, 0.12)	0.53 (0.48, 0.59)	93 (89, 97)	63 (56, 71)	63 (56, 71)	67 (60, 75)
		multivariate imputation	0.08 (0.07, 0.10)	0.15 (0.14, 0.17)	63 (52, 73)	57 (48, 66)	58 (48, 67)	60 (51, 69)
		univariate imputation	0.07 (0.05, 0.08)	0.07 (0.07, 0.08)	40 (31, 52)	63 (54, 72)	63 (54, 73)	67 (58, 76)
		rolling GAM	0.08 (0.06, 0.10)	0.20 (0.07, 0.32)	77 (31, 95)	53 (36, 67)	53 (36, 67)	53 (35, 70)
		global GAM	0.05 (0.03, 0.07)	0.10 (0.02, 0.15)	74 (15, 95)	76 (54, 88)	76 (52, 88)	85 (58, 94)

## S9 Plateau Classification by Simulation Scenario

Because the simulated true trend and its rate of change are known exactly, there is no directly equivalent definition available to classify true plateaus for the simulated trend to evaluate multiclass performance. However, applying the standard plateau definition (non-significant slope at a 5% significance level) to the simulation study estimates, we observed notable differences between methods in the proportion of estimates classified as plateaus, particularly under the less-smooth scenarios (Figure S5).

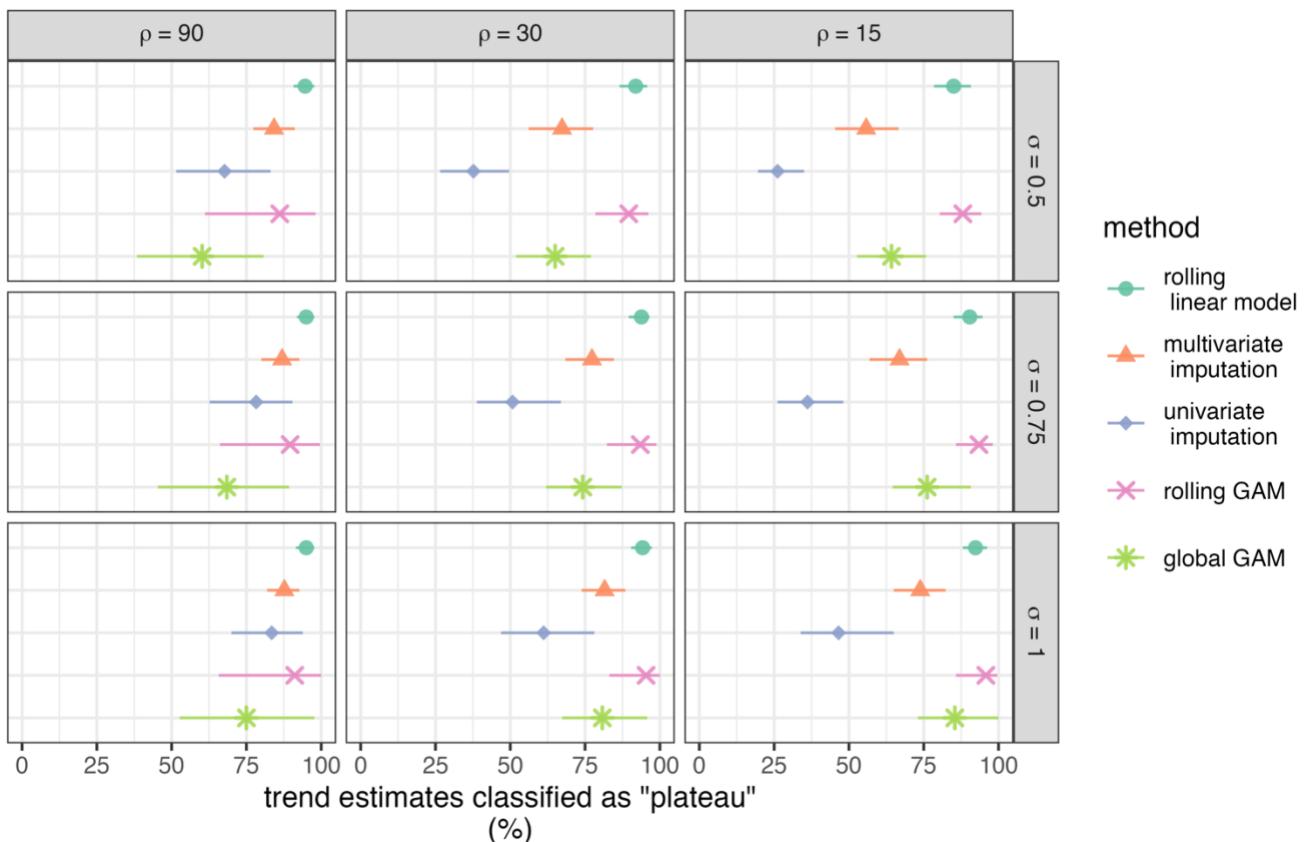


Figure S5. Median and 2.5<sup>th</sup> – 97.5<sup>th</sup> percentiles of the percentage of estimates classified as plateau (not significantly different from zero at the 5% significance level) by each rate of change estimation method across 1000 realizations of each of the nine simulation scenarios.

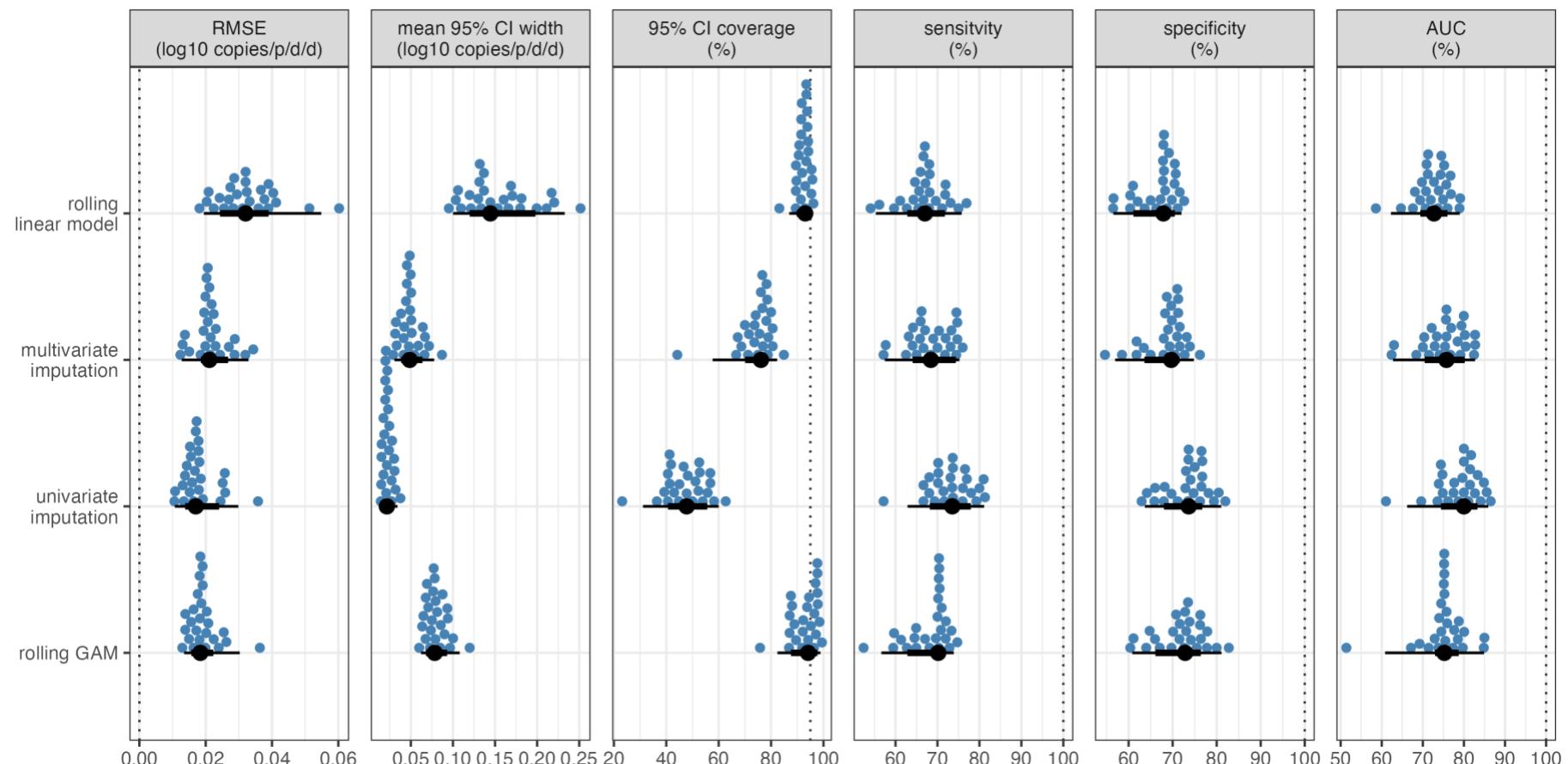
## S10 North Carolina Sewershed Characteristics

Table S2. Characteristics of North Carolina Sewersheds

Sewershed	County	Population Served	Monitoring Start Date	Days Monitored <sup>a</sup>	Samples Reported	Median (IQR) Daily Reported Cases	Median (IQR) Per-Capita Viral Load, million gene copies/person/day
Beaufort	Carteret	3500	2021-01-03	871	245	1 (3)	6.7 (18.5)
Buncombe Co.	Buncombe, Henderson	173000	2021-06-19	704	185	36 (48)	9.9 (11.3)
Cary 1	Wake	84189	2021-11-16	554	157	13 (23)	12.8 (18.5)
Cary 2	Wake	74331	2021-11-16	554	156	9 (18)	17.5 (17.9)
Cary 3	Wake	75886	2021-11-16	554	149	15 (30)	36.8 (44.3)
Chapel Hill - Carrboro	Orange	78141	2021-01-06	868	238	11 (17)	6.3 (11.7)
Charlotte 1	Mecklenburg	68685	2021-01-03	871	226	14 (22)	11.3 (15.3)
Charlotte 2	Mecklenburg	182501	2021-01-03	871	226	27 (39)	10.0 (14.6)
Charlotte 3	Mecklenburg	120000	2021-06-01	722	189	25 (38)	17.9 (24.4)
Durham	Durham	108105	2021-01-06	868	240	16 (25)	8.6 (14.5)
Fayetteville	Cumberland	151589	2021-06-19	704	198	33 (49)	10.1 (11.0)
Greensboro	Guilford	135821	2021-06-18	705	193	25 (34)	9.8 (14.0)
Greenville	Pitt	89616	2021-01-03	871	242	17 (26)	7.1 (11.8)
Jacksonville	Onslow	41819	2022-03-19	431	121	5 (9)	5.7 (8.9)
Laurinburg	Scotland	15527	2021-06-17	706	186	3 (6)	6.9 (12.0)
Marion	McDowell	8459	2021-06-17	706	191	2 (4)	5.6 (10.7)
New Hanover Co.	New Hanover	67743	2021-01-22	852	235	7 (12)	5.0 (10.5)
Raleigh 1	Wake	550000	2021-01-06	868	231	100 (146)	7.0 (10.6)
Raleigh 2	Wake	30655	2021-10-21	580	160	8 (15)	10.8 (15.1)
Raleigh 3	Wake	7776	2021-10-21	580	158	2 (4)	15.8 (25.8)
Roanoke Rapids	Halifax, Northampton	14320	2021-06-19	704	194	4 (7)	9.3 (14.2)
Tuckaseigee	Jackson	13296	2021-01-03	871	213	2 (3)	4.0 (8.1)
Wilmington	New Hanover	58361	2021-01-05	869	235	9 (15)	3.7 (7.6)
Wilson	Wilson	49384	2021-06-19	704	194	8 (14)	6.2 (12.1)
Winston-Salem	Forsyth	178000	2021-06-19	704	186	38 (54)	5.3 (6.2)

<sup>a</sup> monitoring ended for all sewersheds on 2023-05-24

1    S11    Relative Performance of Estimation Methods in NC Sewersheds



2  
3    Figure S6. Comparison of rate of change estimates from local estimation methods to global GAM estimates for SARS-CoV-2 wastewater  
4    viral loads at 25 NC sewersheds. Each blue point corresponds to a sewersheds, with the black point and line presenting the median and 2.5<sup>th</sup> –  
5    97.5<sup>th</sup> percentiles of the performance metric across sewersheds for a given local estimation method. Vertical dotted lines indicate the target  
6    performance for each metric

7 **S12 Trend Classifications in NC Sewersheds**

8 Table S3. Percentage of rate of change estimates classified as positive (two class) and increasing, decreasing, or plateau (three class) in North  
9 Carolina sewersheds by estimation method

Sewersheds	N	Positive Slope (% of estimates)					Slope Classification <sup>a</sup> (% of estimates)											
		Global GAM				RLM			MI			UI			Rolling GAM			
		↑	↓	—	↑	↓	—	↑	↓	—	↑	↓	—	↑	↓	—		
Beaufort	219	51	49	52	52	49	6	6	88	5	3	92	12	10	78	26	26	
Buncombe Co.	160	44	51	51	49	48	11	11	79	7	8	86	14	19	67	30	31	
Cary 1	133	43	50	44	49	43	11	6	83	5	8	88	12	14	74	29	28	
Cary 2	132	34	45	44	42	36	14	5	80	0	5	95	17	20	64	24	36	
Cary 3	130	36	44	47	42	42	16	8	76	5	5	89	18	16	66	29	45	
Chapel Hill - Carrboro	213	43	47	49	48	46	16	11	72	3	5	92	15	18	67	28	32	
Charlotte 1	201	48	48	51	48	45	14	11	75	6	5	89	17	13	70	32	35	
Charlotte 2	201	45	49	51	48	44	14	12	74	3	2	95	17	19	64	29	35	
Charlotte 3	165	49	46	47	48	48	15	13	73	4	5	91	19	22	58	32	38	
Durham	216	46	52	48	50	46	15	11	74	7	3	90	12	16	71	28	26	
Fayetteville	172	44	47	44	42	40	13	13	74	4	5	91	14	16	70	26	37	
Greensboro	167	40	46	45	47	47	9	8	83	8	5	87	10	13	77	23	27	
Greenville	217	47	48	49	47	43	18	16	66	6	6	88	18	21	61	29	36	
Jacksonville	95	44	45	48	45	45	0	1	99	6	15	79	15	25	60	36	44	
Laurinburg	160	45	48	45	48	51	11	10	79	4	4	92	15	15	70	29	35	
Marion	165	47	48	49	42	49	12	15	73	4	7	90	9	15	76	30	33	
New Hanover Co.	209	44	55	50	45	44	16	6	78	3	2	95	14	15	71	25	27	
Raleigh 1	207	48	52	52	51	48	18	14	68	9	6	85	13	21	66	33	33	
Raleigh 2	138	41	46	46	46	45	9	14	78	1	12	88	13	20	67	24	36	
Raleigh 3	139	41	42	47	49	46	10	11	79	7	4	88	11	17	73	27	31	
Roanoke Rapids	170	38	49	44	45	41	12	11	77	4	4	93	8	15	77	18	29	
Tuckaseigee	200	50	53	50	56	52	12	10	77	7	6	87	14	10	76	35	26	
Wilmington	213	43	50	49	44	43	15	9	75	4	4	92	15	17	67	32	36	
Wilson	169	41	45	45	44	43	9	14	77	7	2	91	14	24	62	24	36	
Winston-Salem	163	50	48	47	52	50	11	12	77	6	4	90	10	20	70	31	32	

10 <sup>a</sup> Out of three CDC classes: increasing (↑), decreasing (↓), and plateau (—)

## S13 Sewershed-Specific Rate of Change Estimates

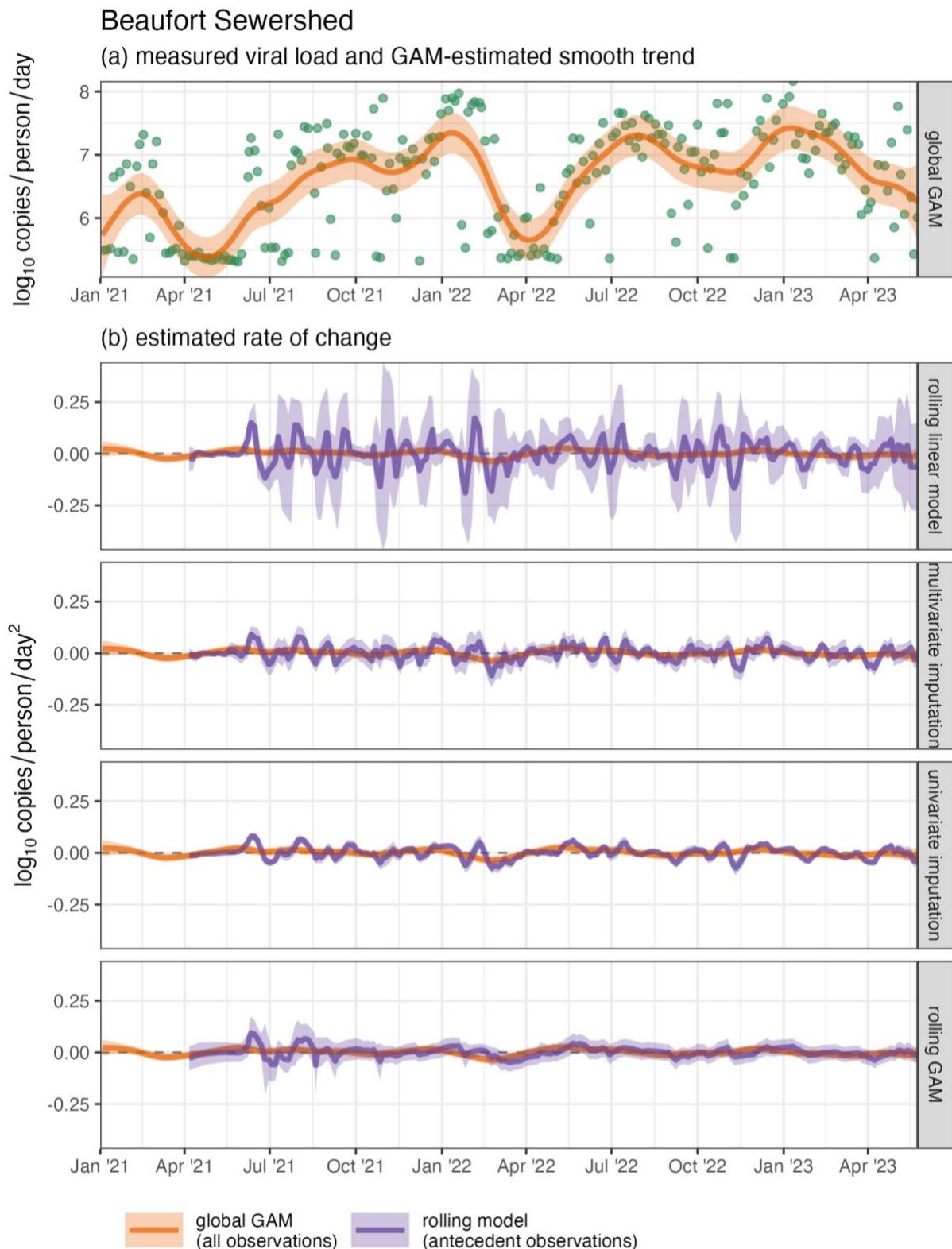
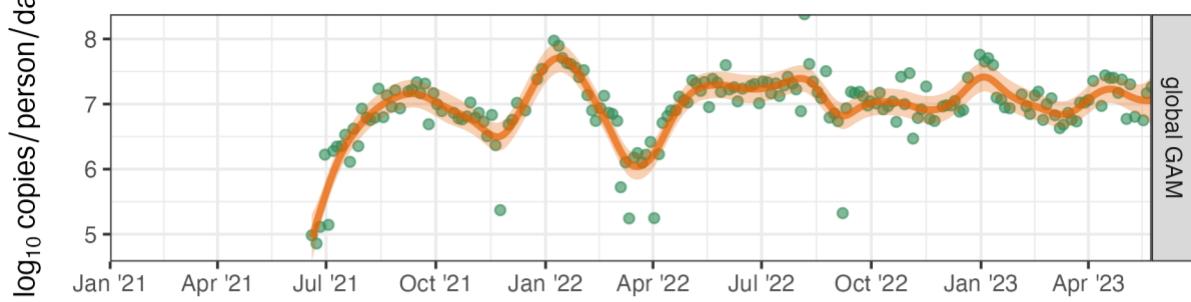


Figure S7. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Beaufort sewershed

## Buncombe Co. Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

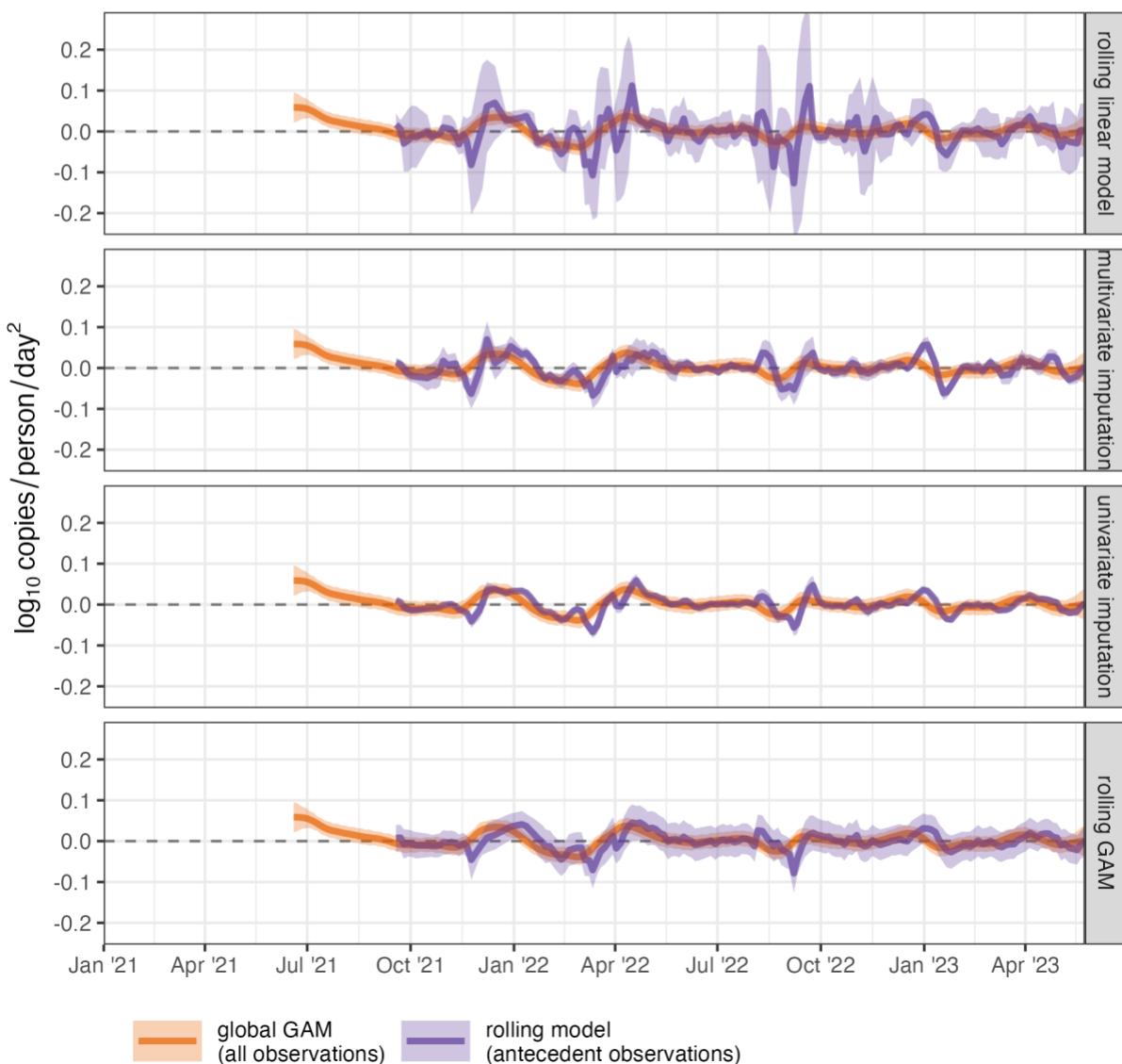
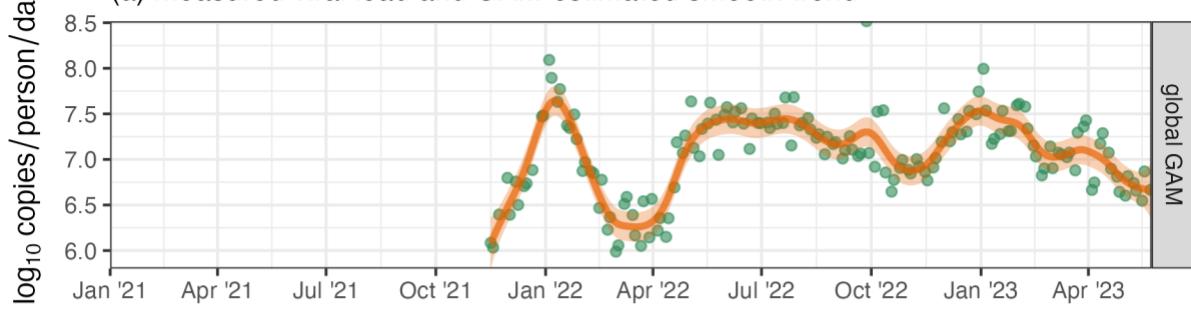


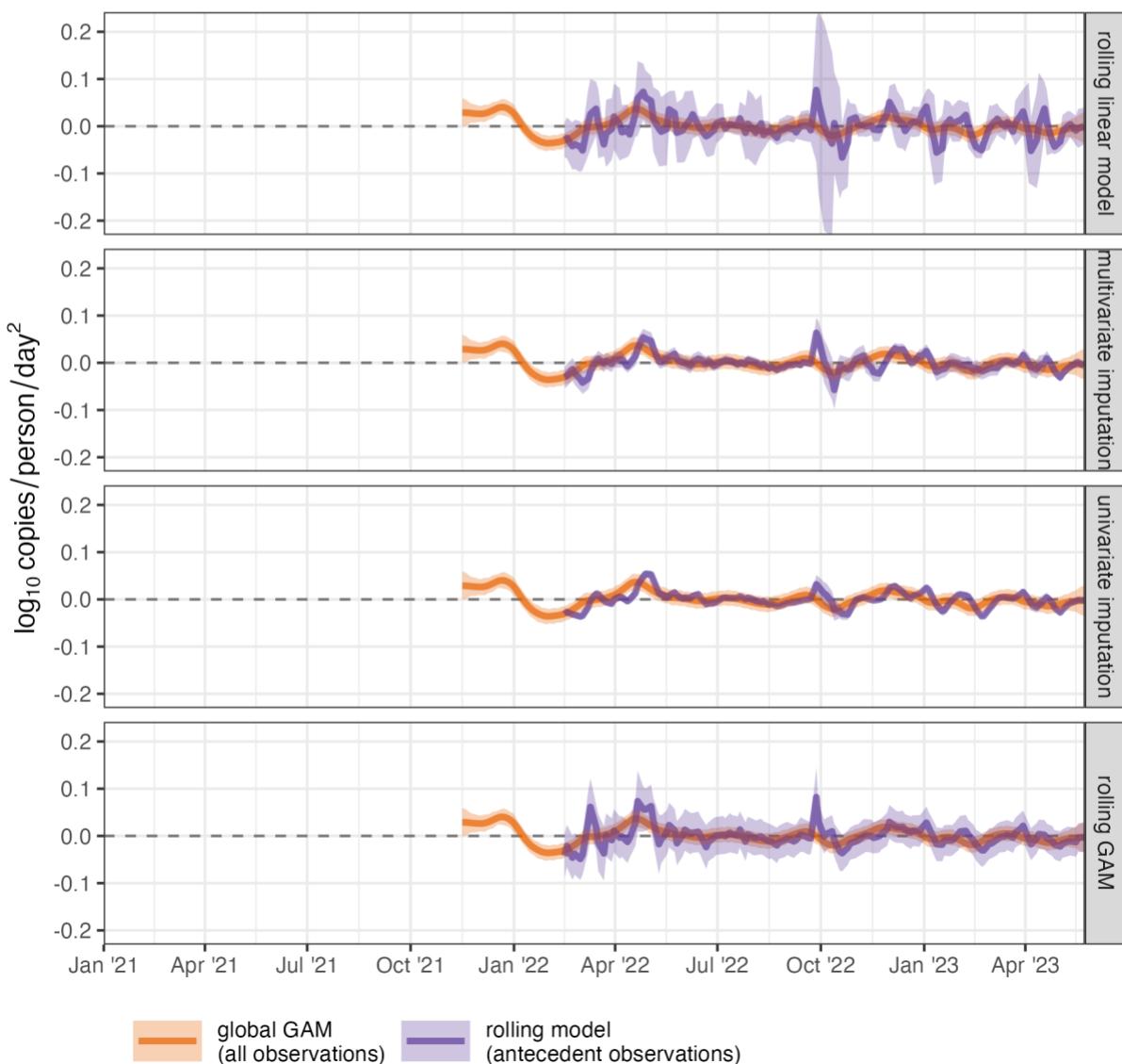
Figure S8. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Buncombe County sewershed

## Cary 1 Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

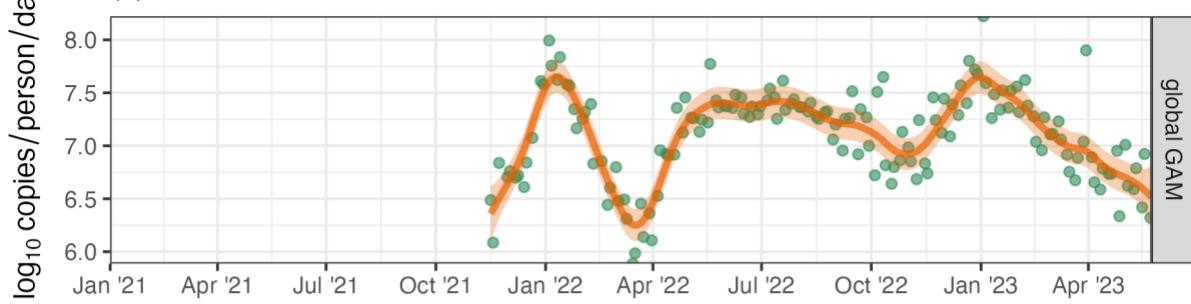


global GAM (all observations)      rolling model (antecedent observations)

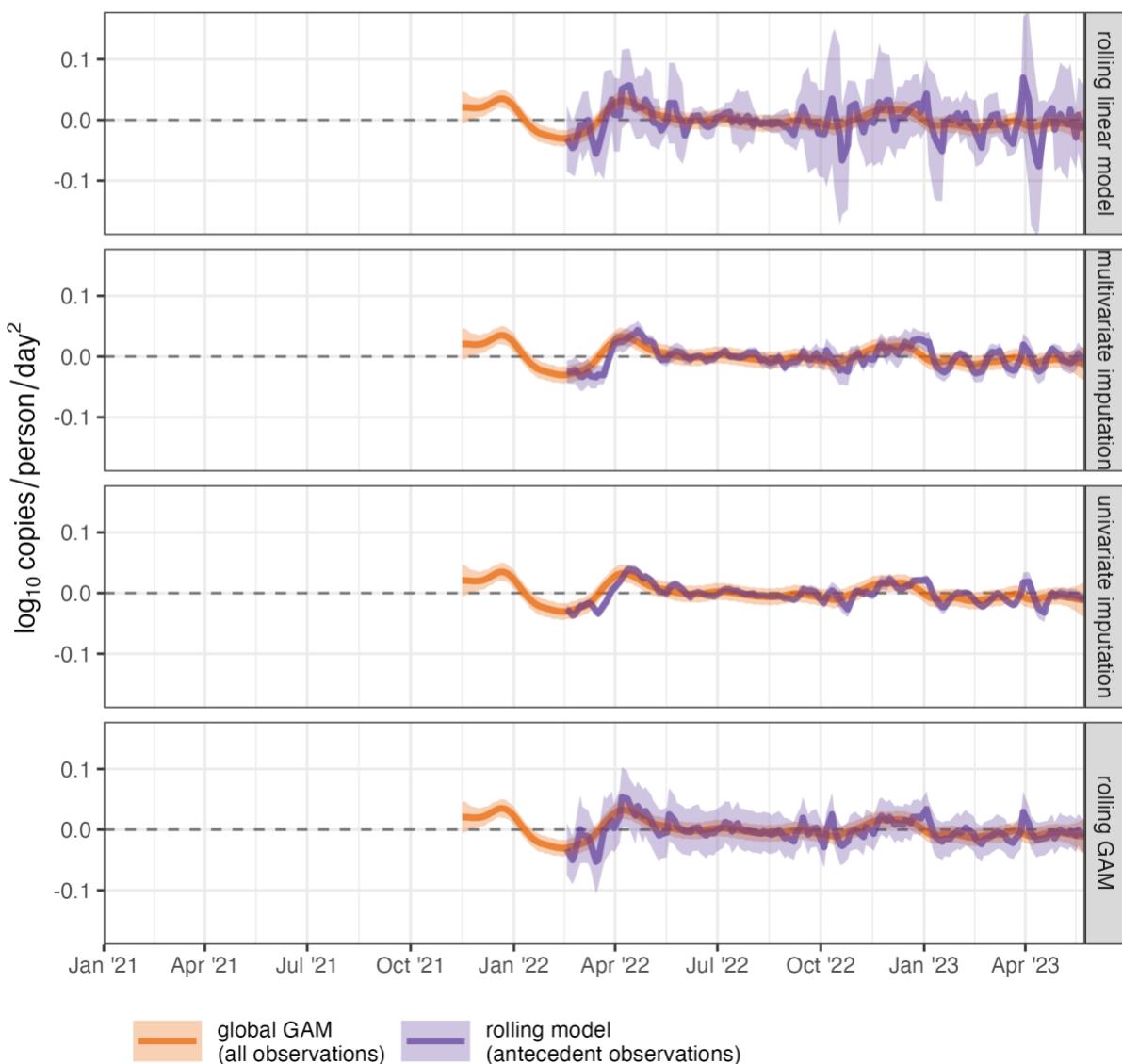
Figure S9. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Cary 1 sewershed

## Cary 2 Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

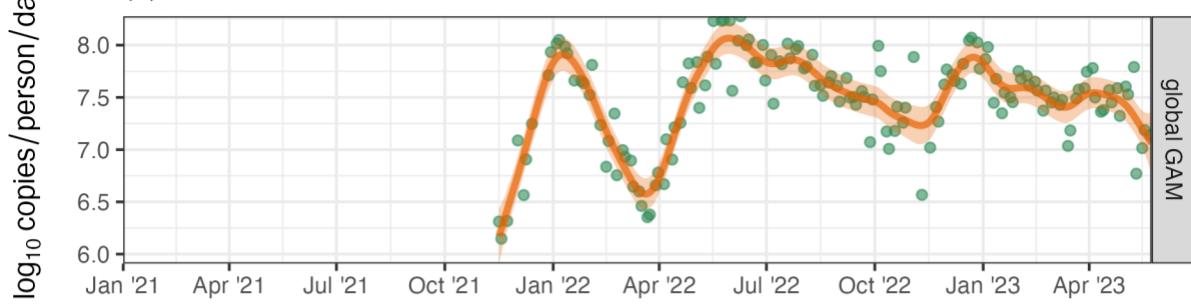


global GAM (all observations)      rolling model (antecedent observations)

Figure S10. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Cary 2 sewershed

## Cary 3 Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

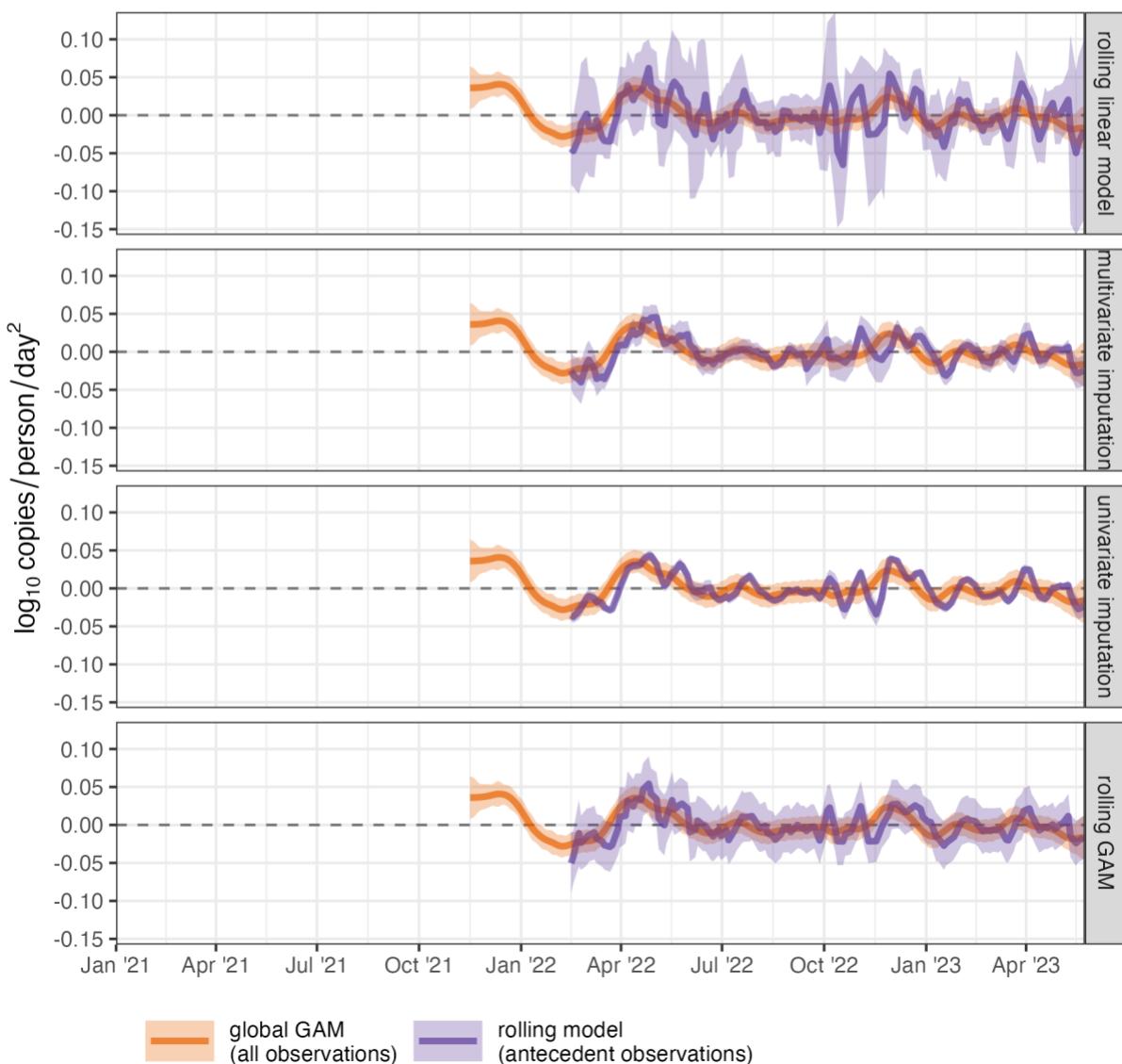
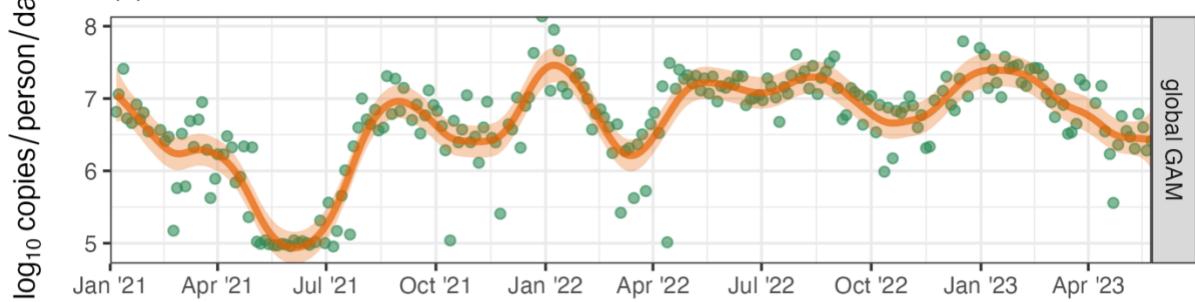


Figure S11. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Cary 3 sewershed

## Chapel Hill - Carrboro Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

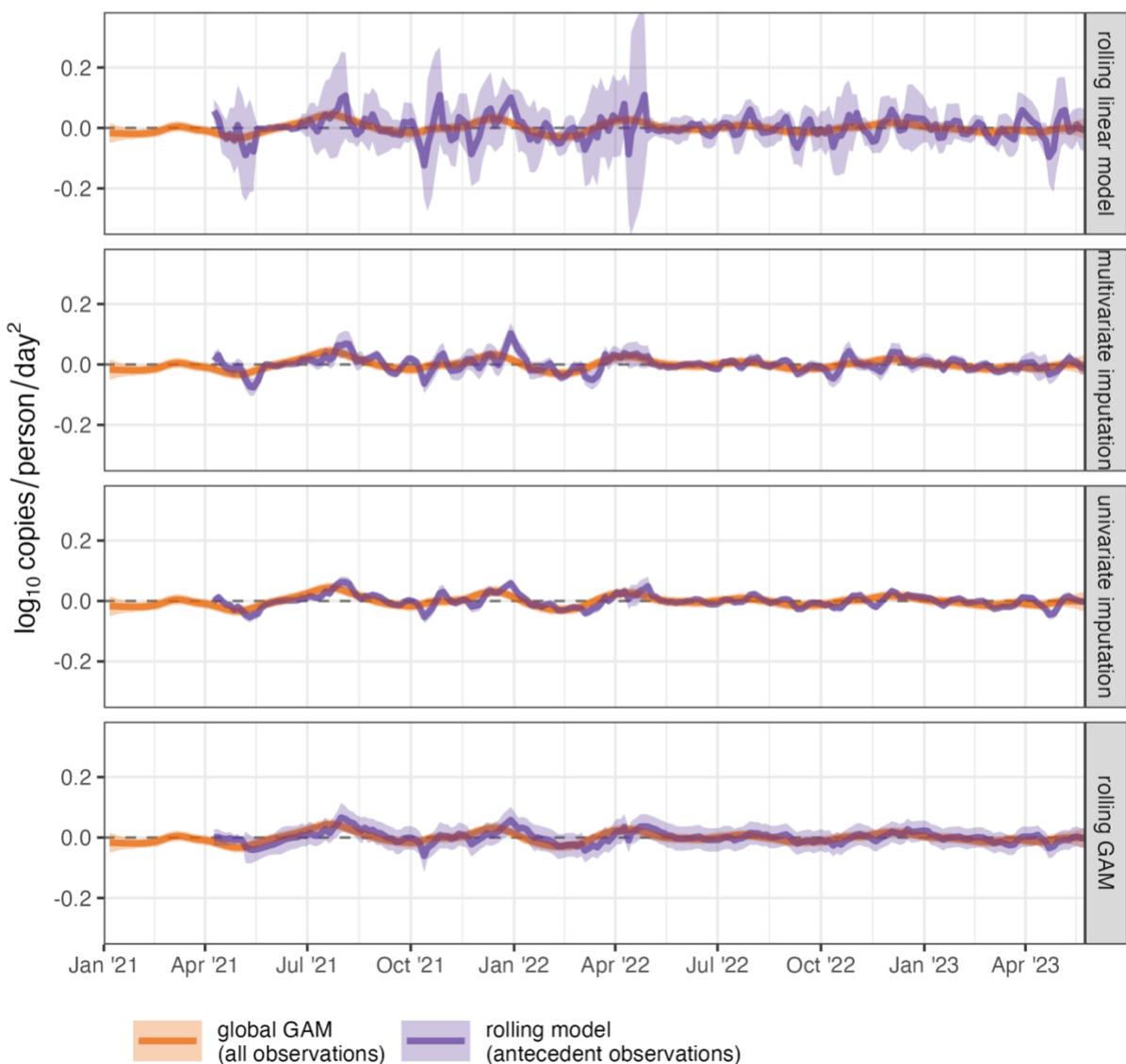
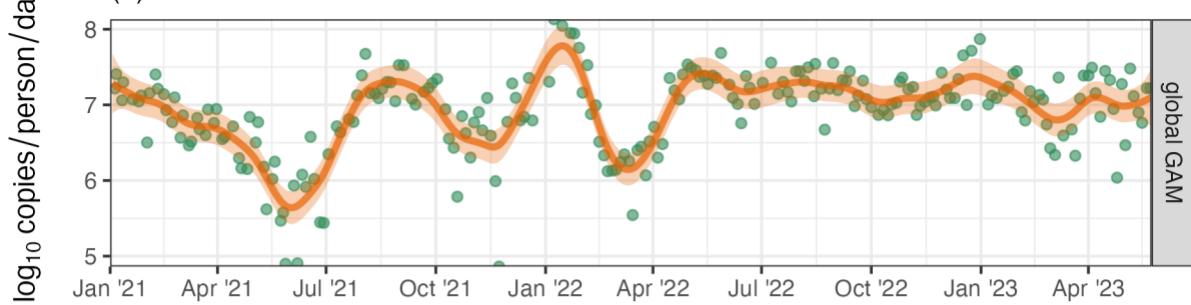


Figure S12. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Chapel Hill – Carrboro sewershed

## Charlotte 1 Sewersheds

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

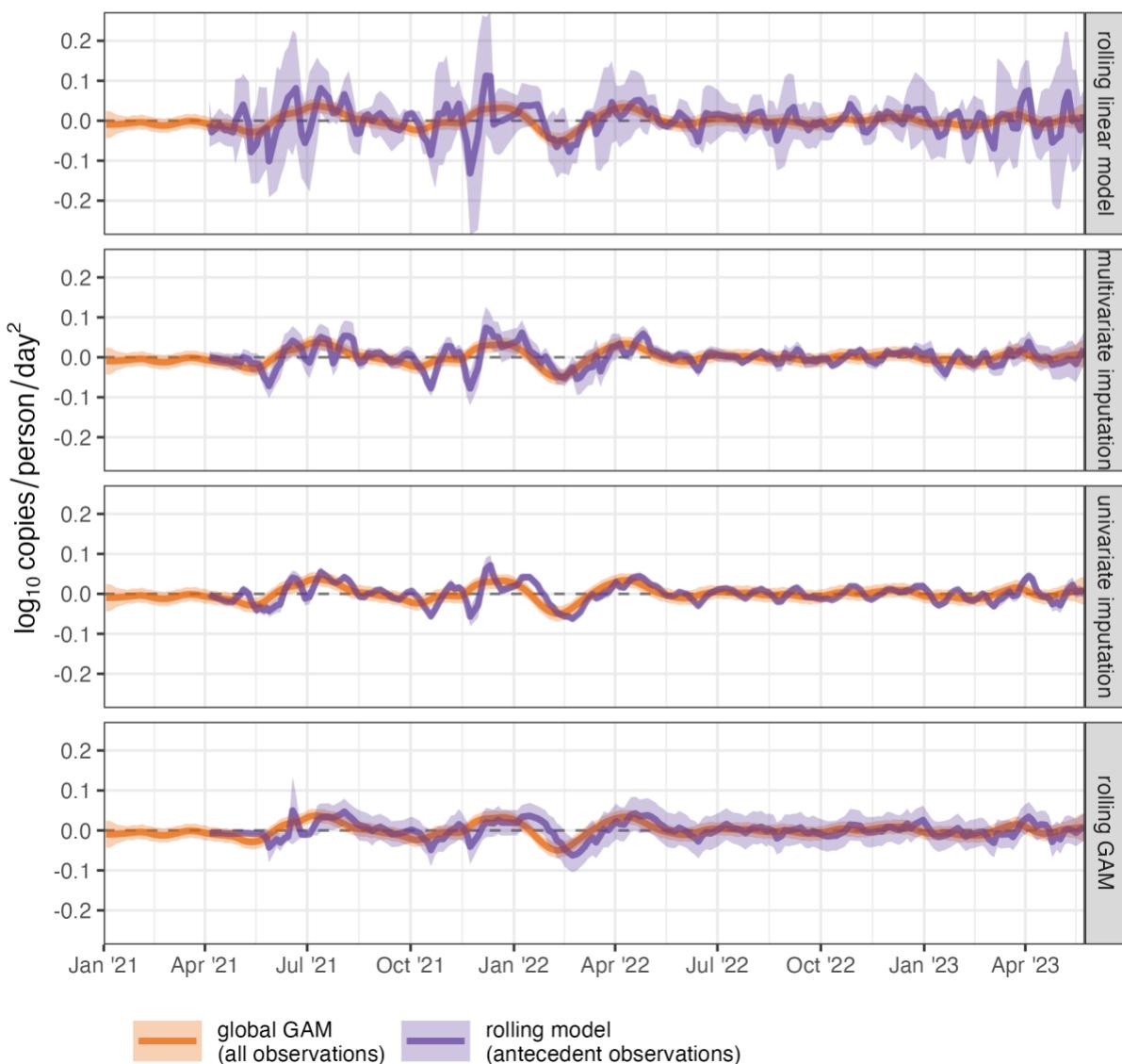
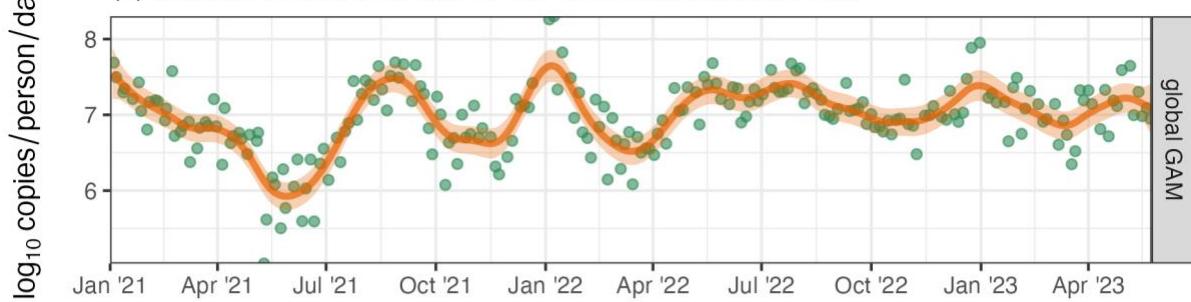


Figure S13. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Charlotte 1 sewersheds

## Charlotte 2 Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

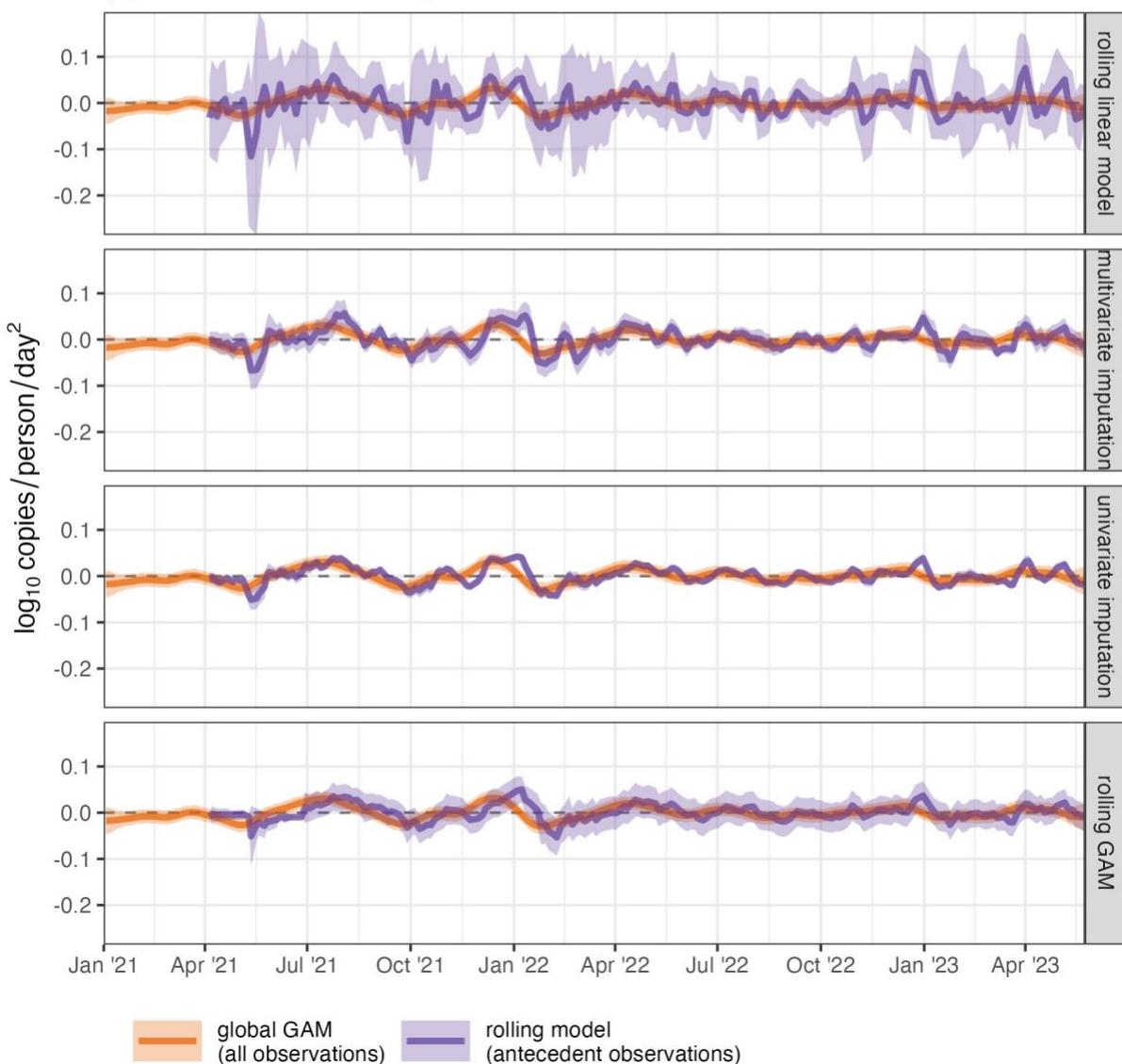
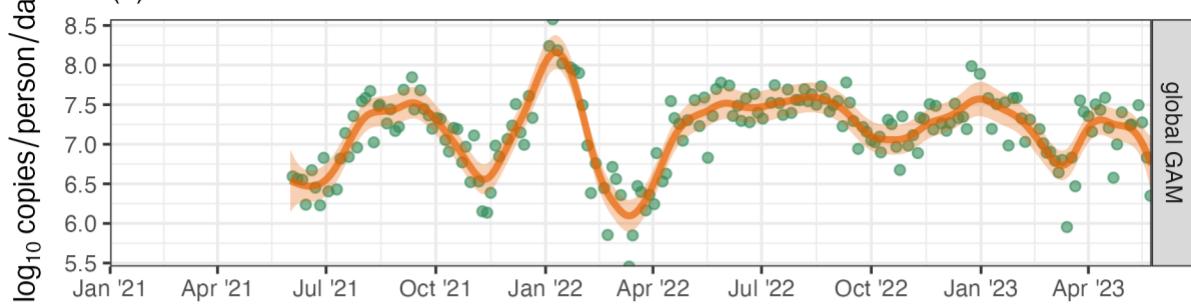


Figure S14. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Charlotte 2 sewershed

## Charlotte 3 Sewersheds

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

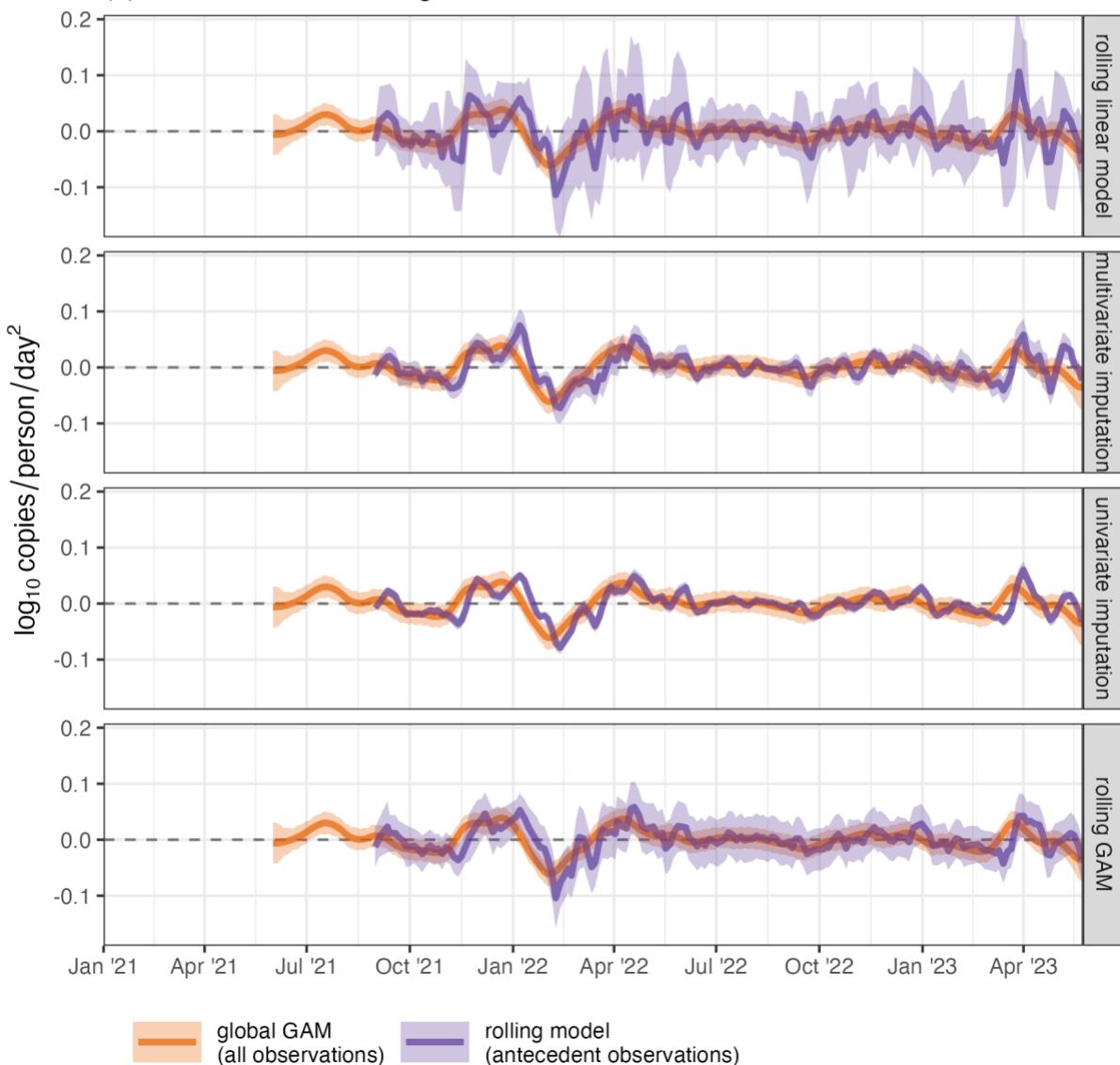
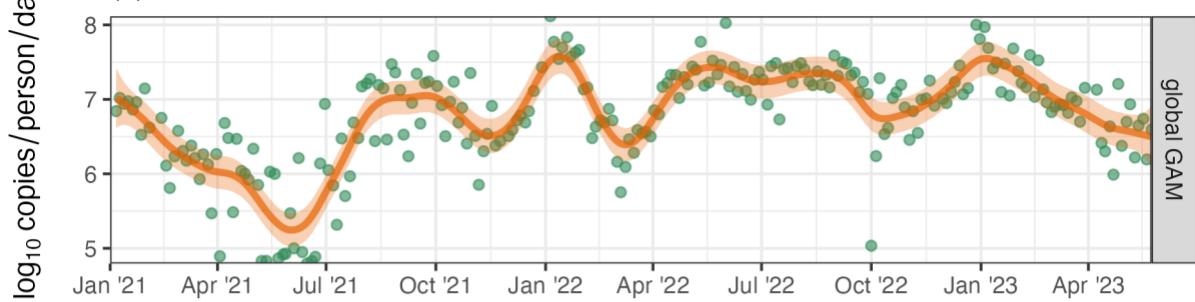


Figure S15. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Charlotte 3 sewersheds

## Durham Sewersheds

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

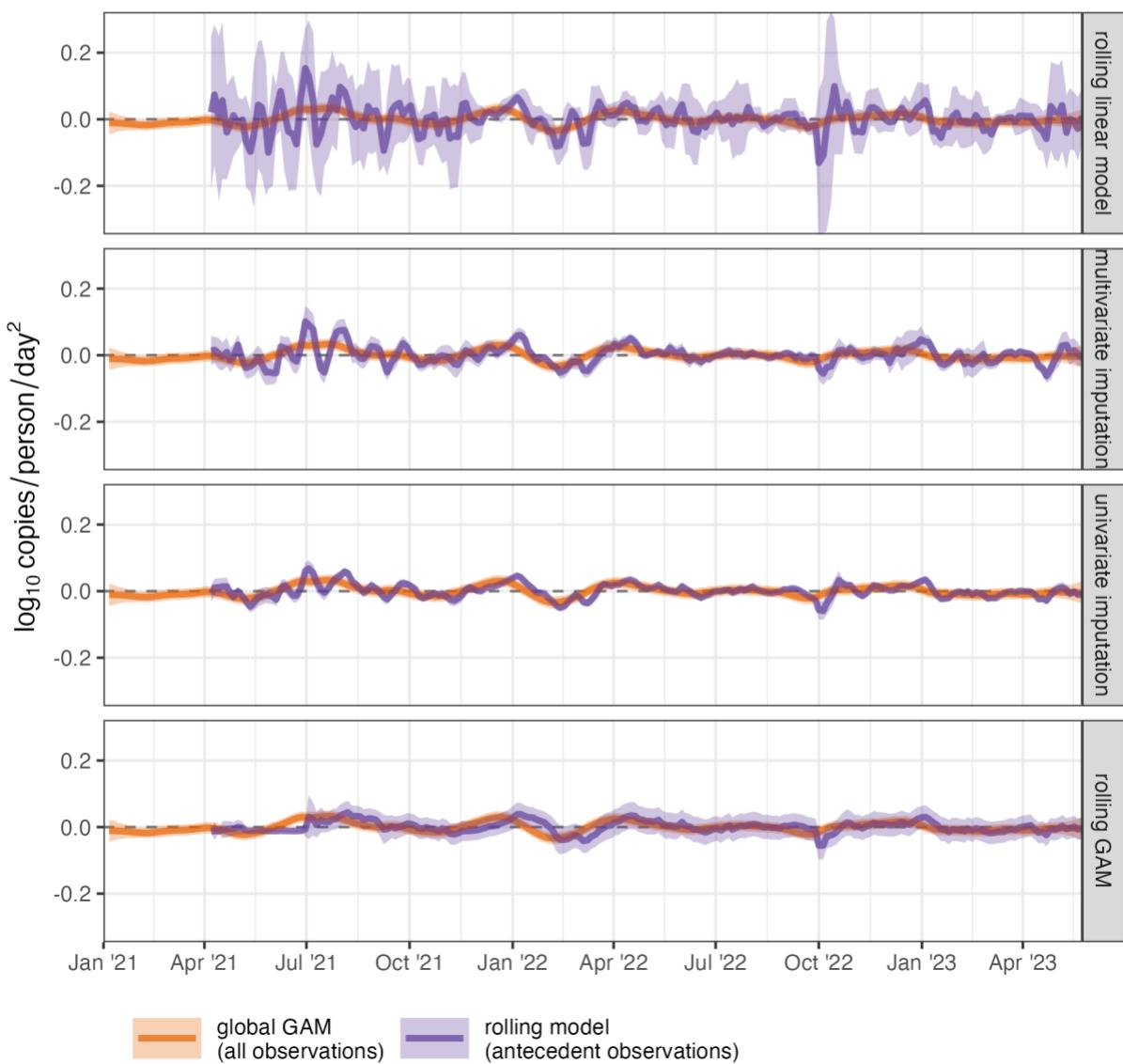
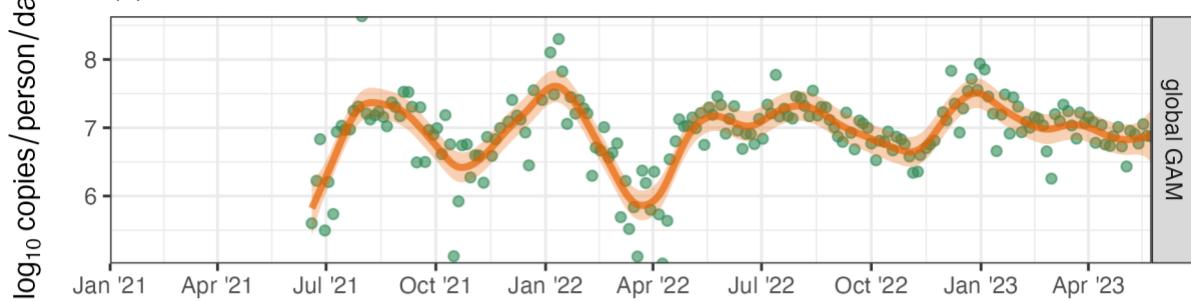


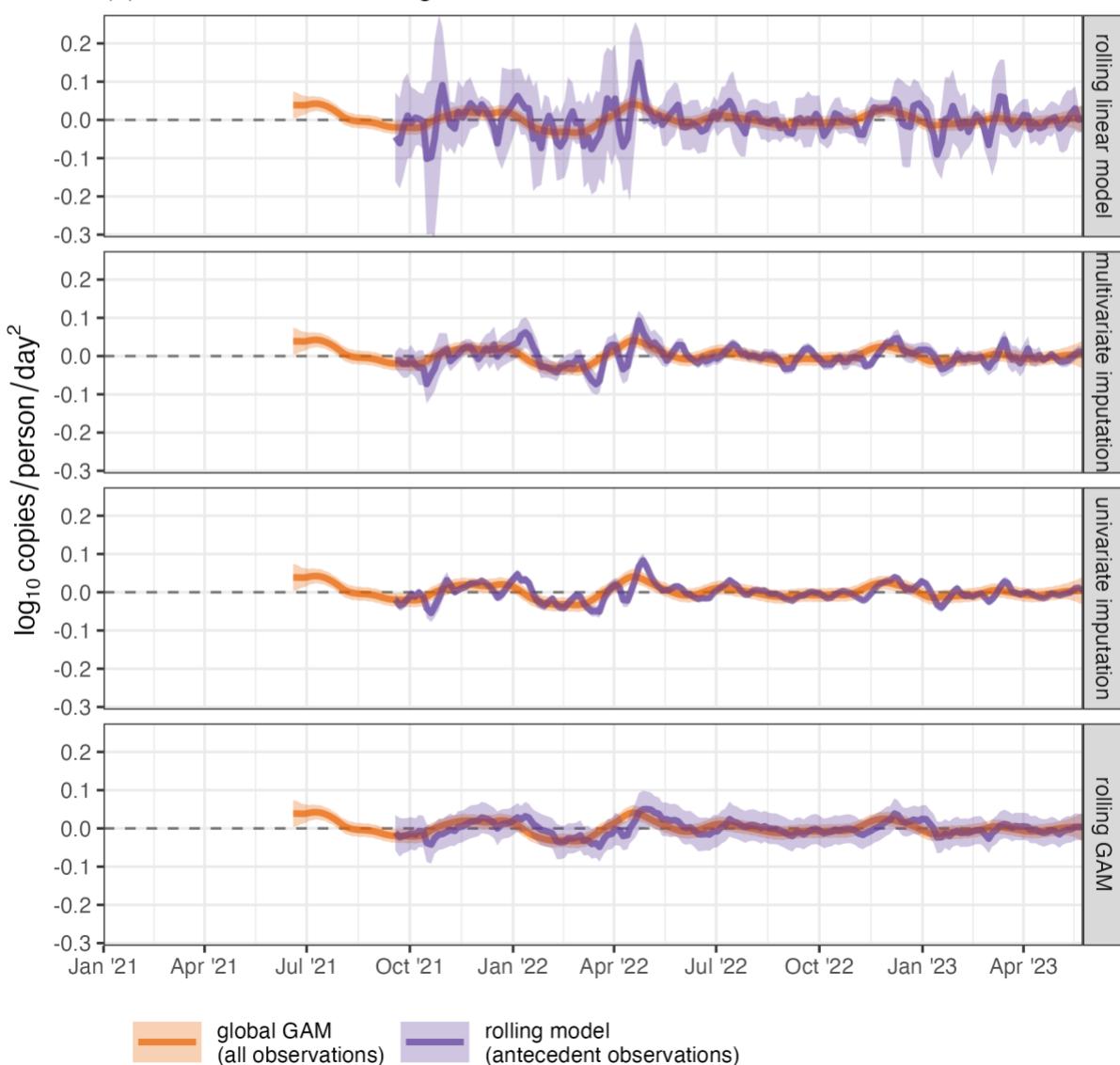
Figure S16. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Durham sewershed

## Fayetteville Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

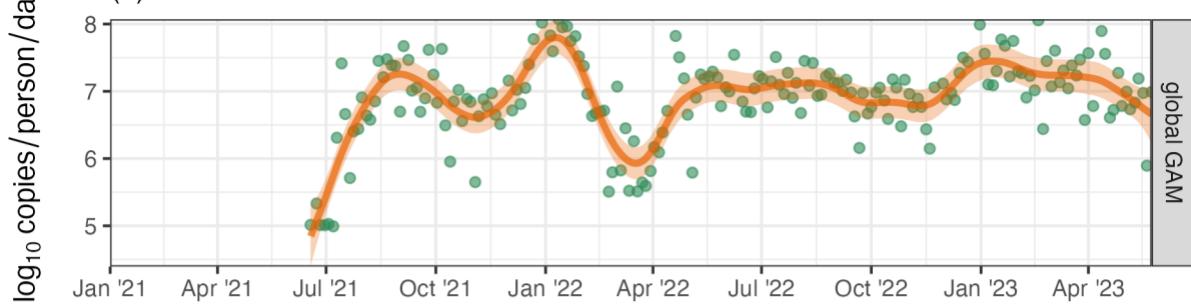


global GAM (all observations)      rolling model (antecedent observations)

Figure S17. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Fayetteville sewershed

## Greensboro Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

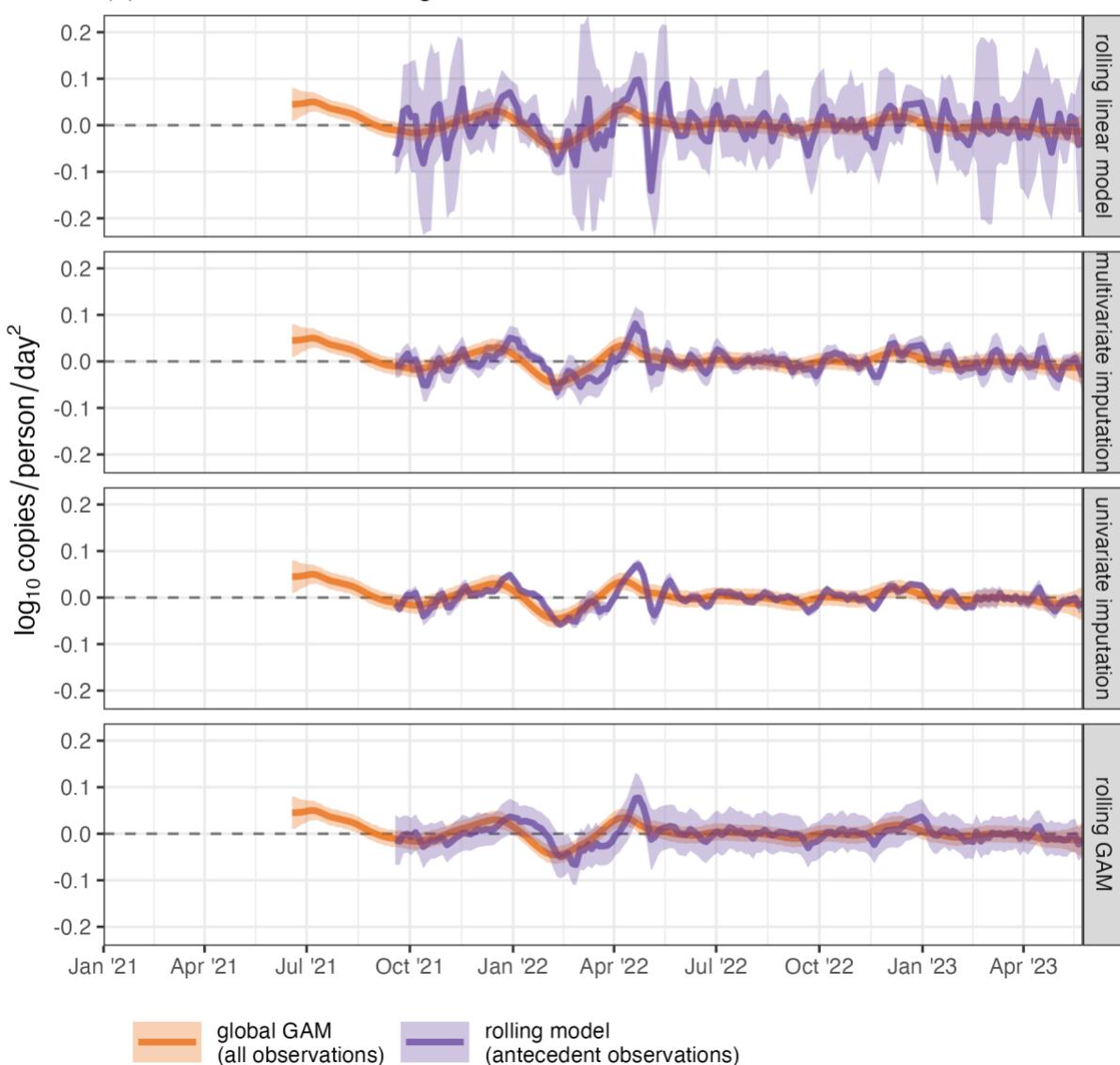
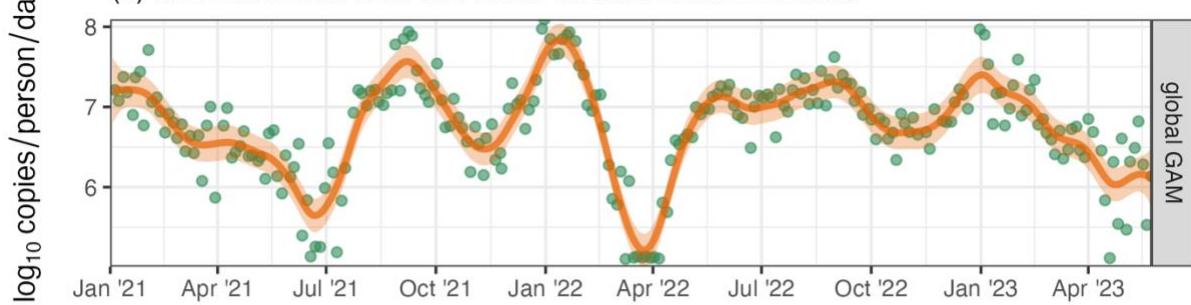


Figure S18. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Greensboro sewershed

## Greenville Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

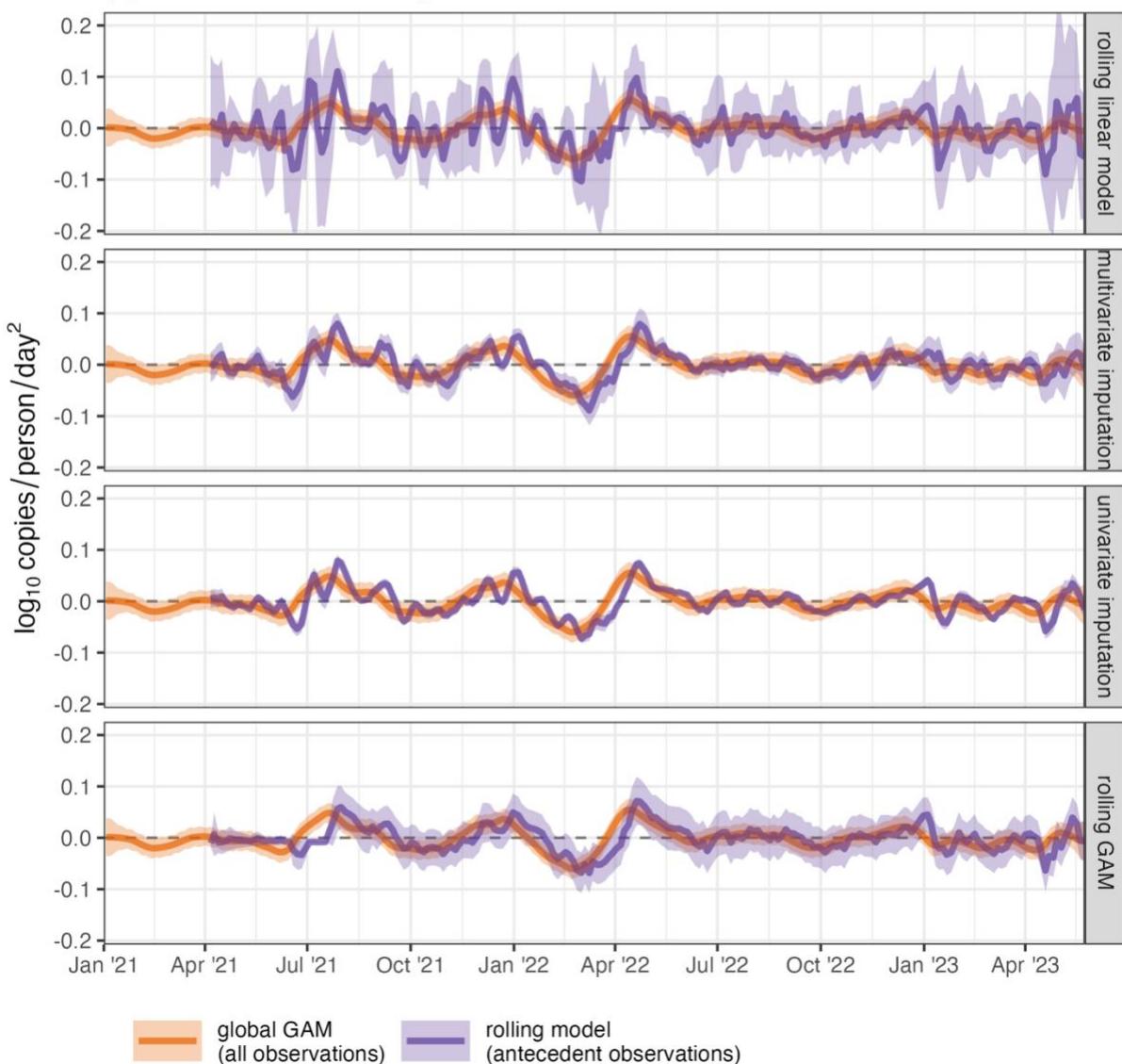
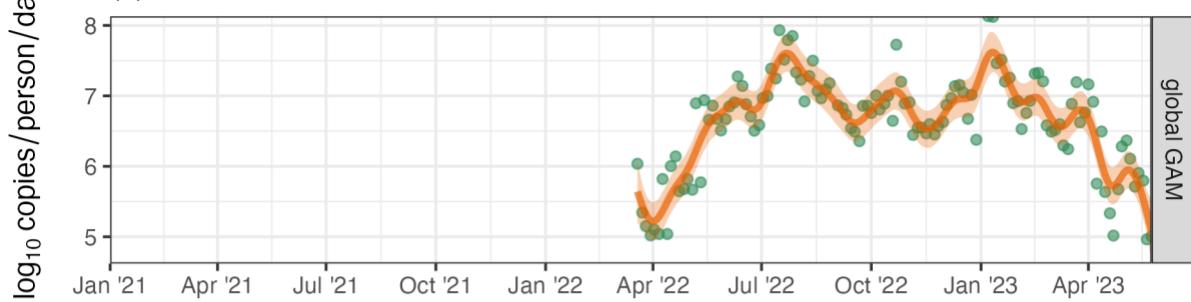


Figure S19. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Greenville sewershed

## Jacksonville Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

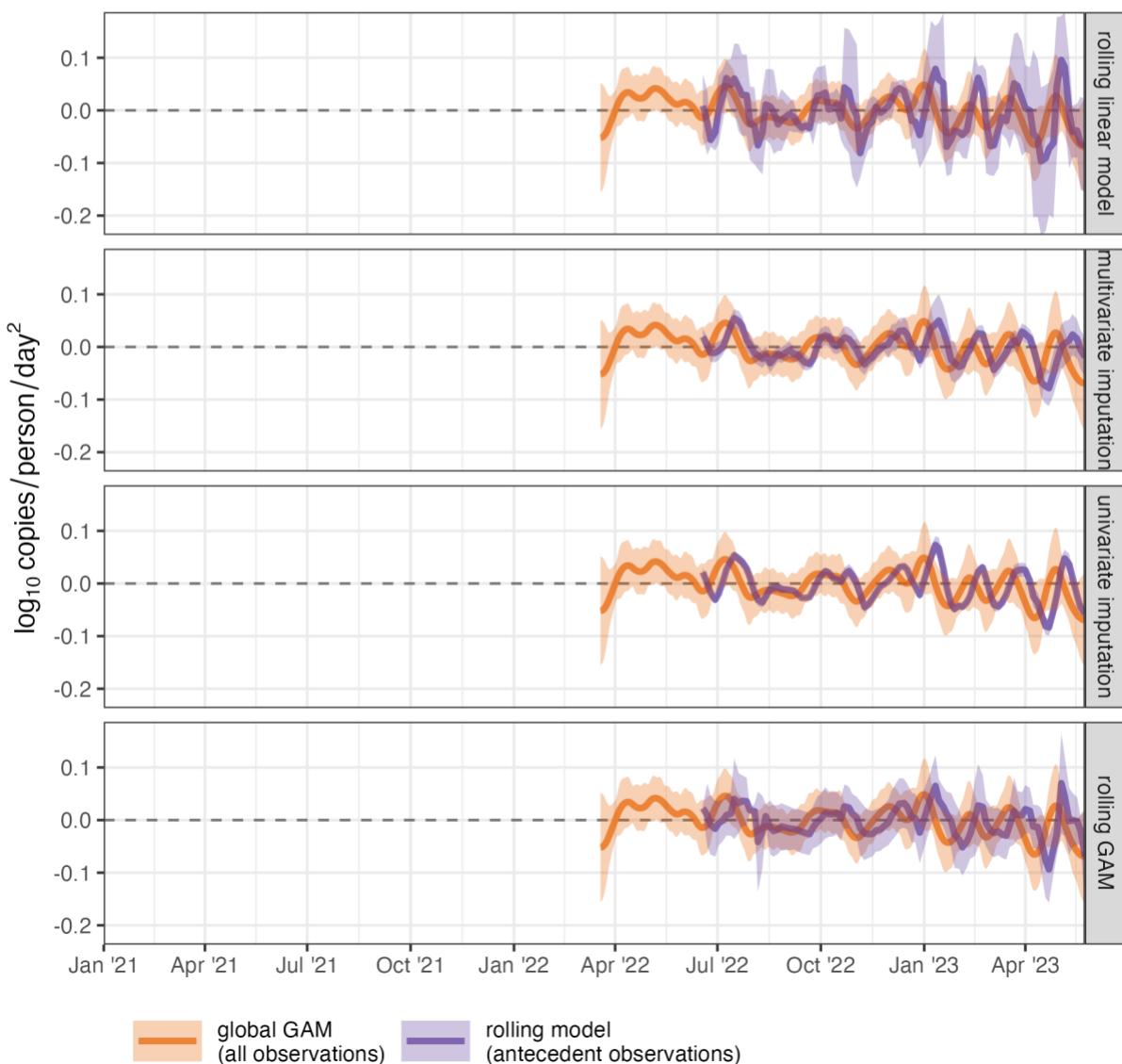
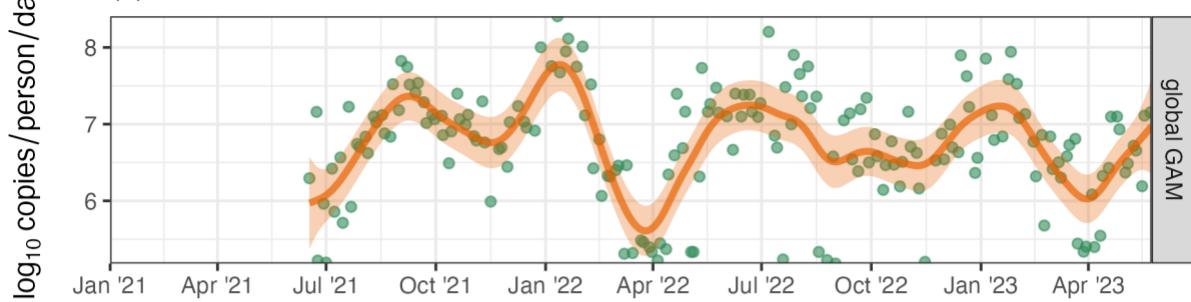


Figure S20. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Jacksonville sewershed

## Laurinburg Sewersheds

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

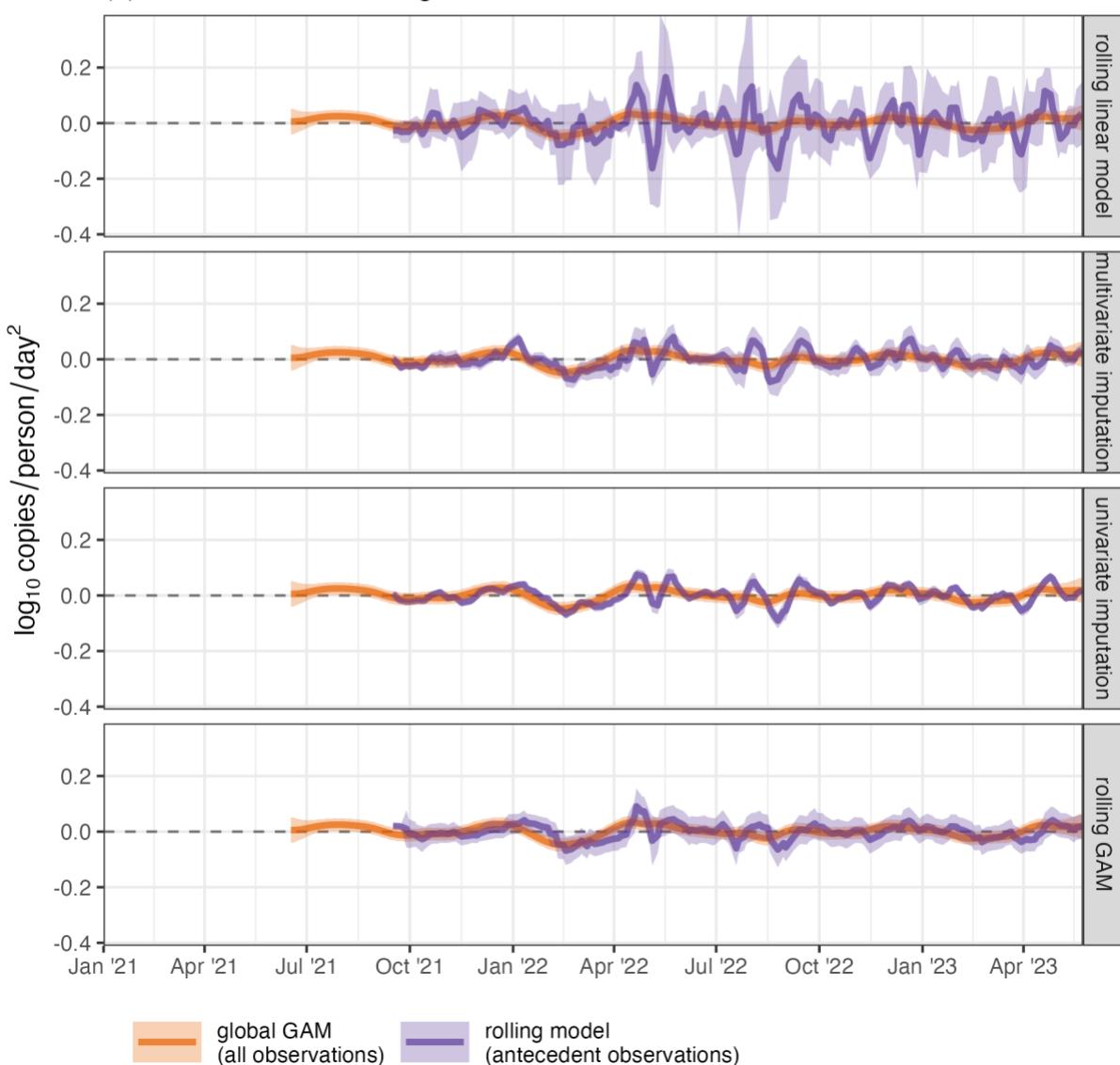
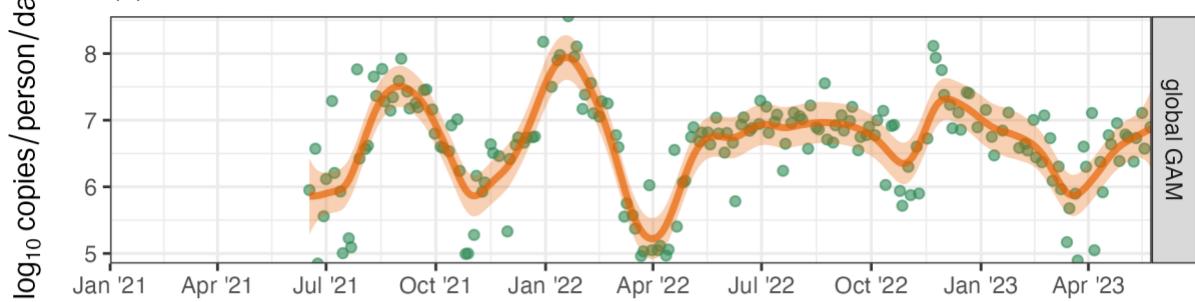


Figure S21. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Laurinburg sewersheds

## Marion Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

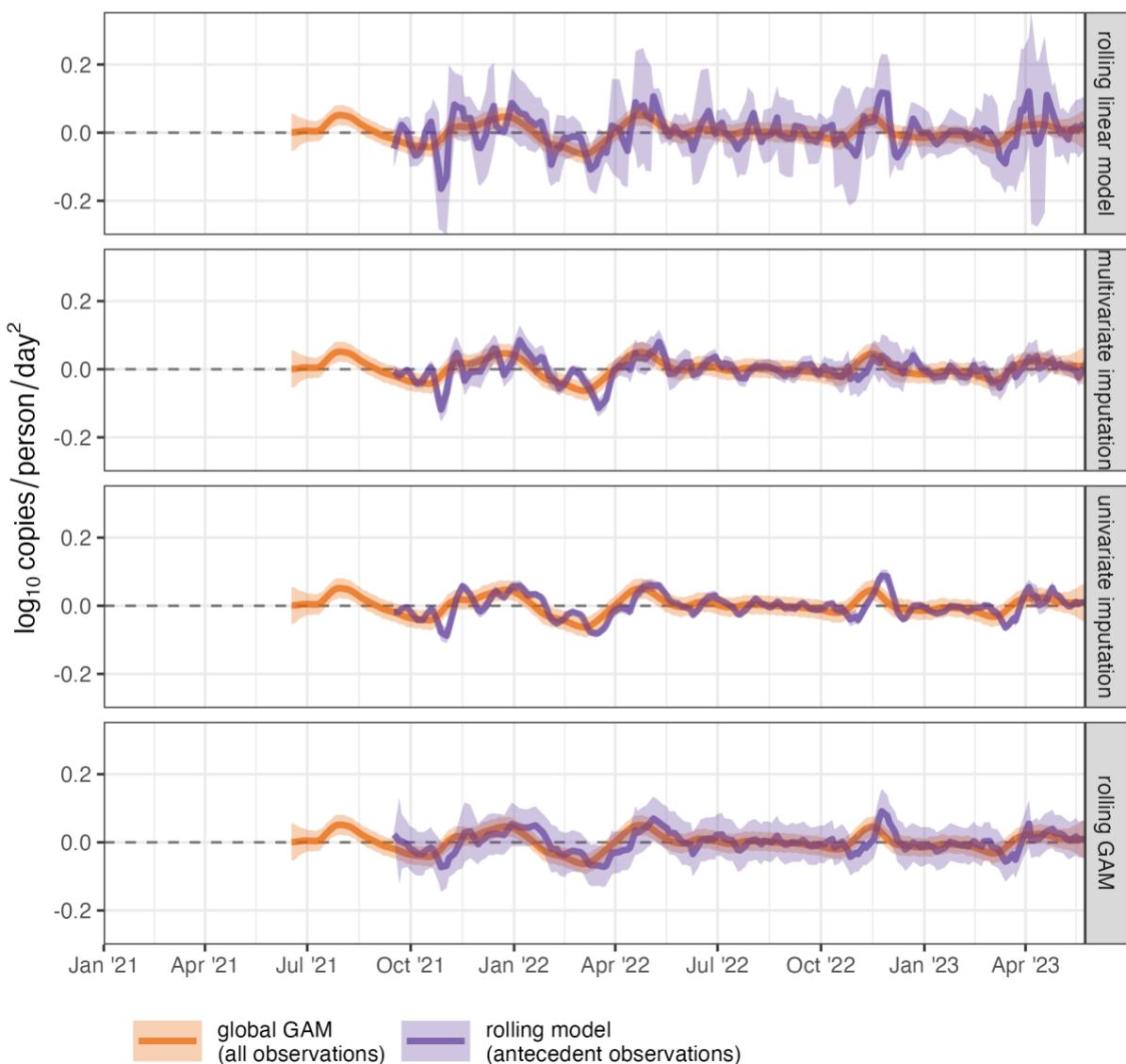
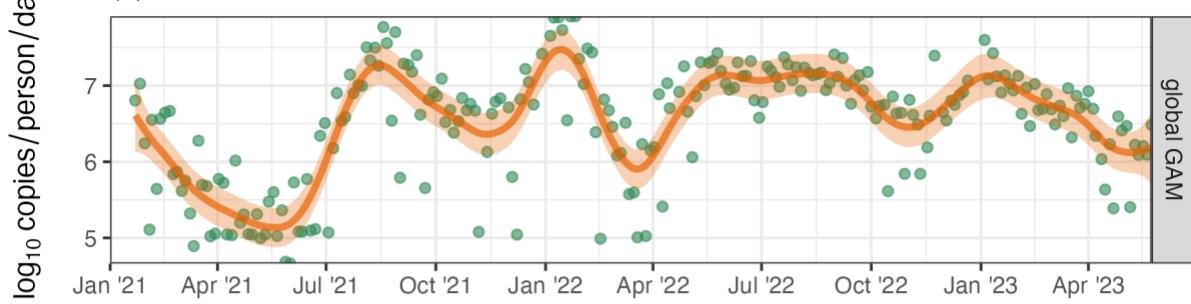


Figure S22. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Marion sewershed

## New Hanover Co. Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

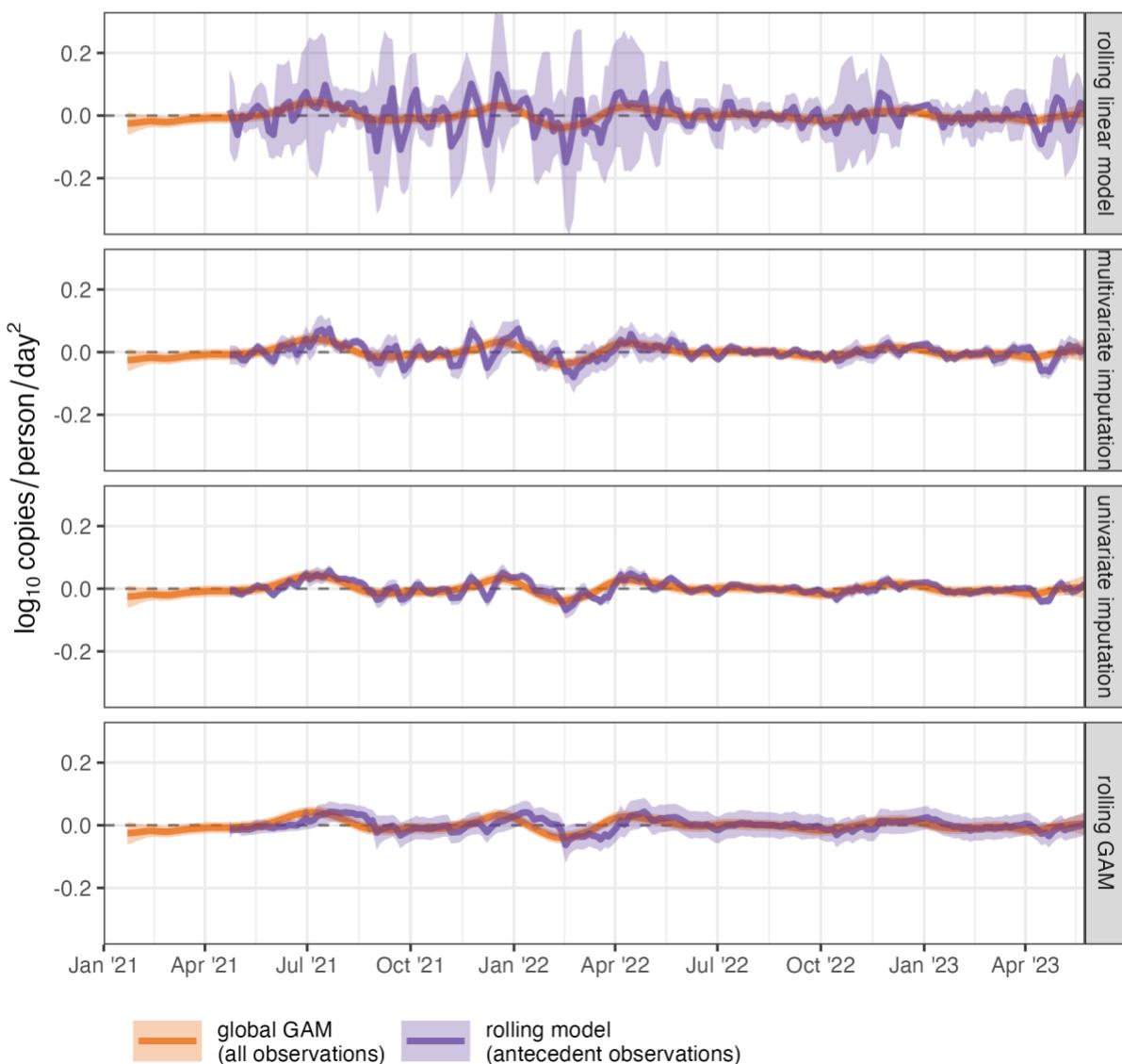
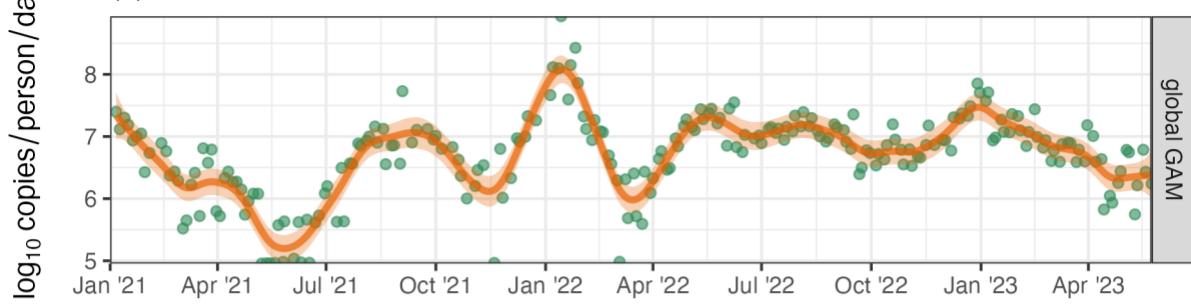


Figure S23. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the New Hanover County sewershed

## Raleigh 1 Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

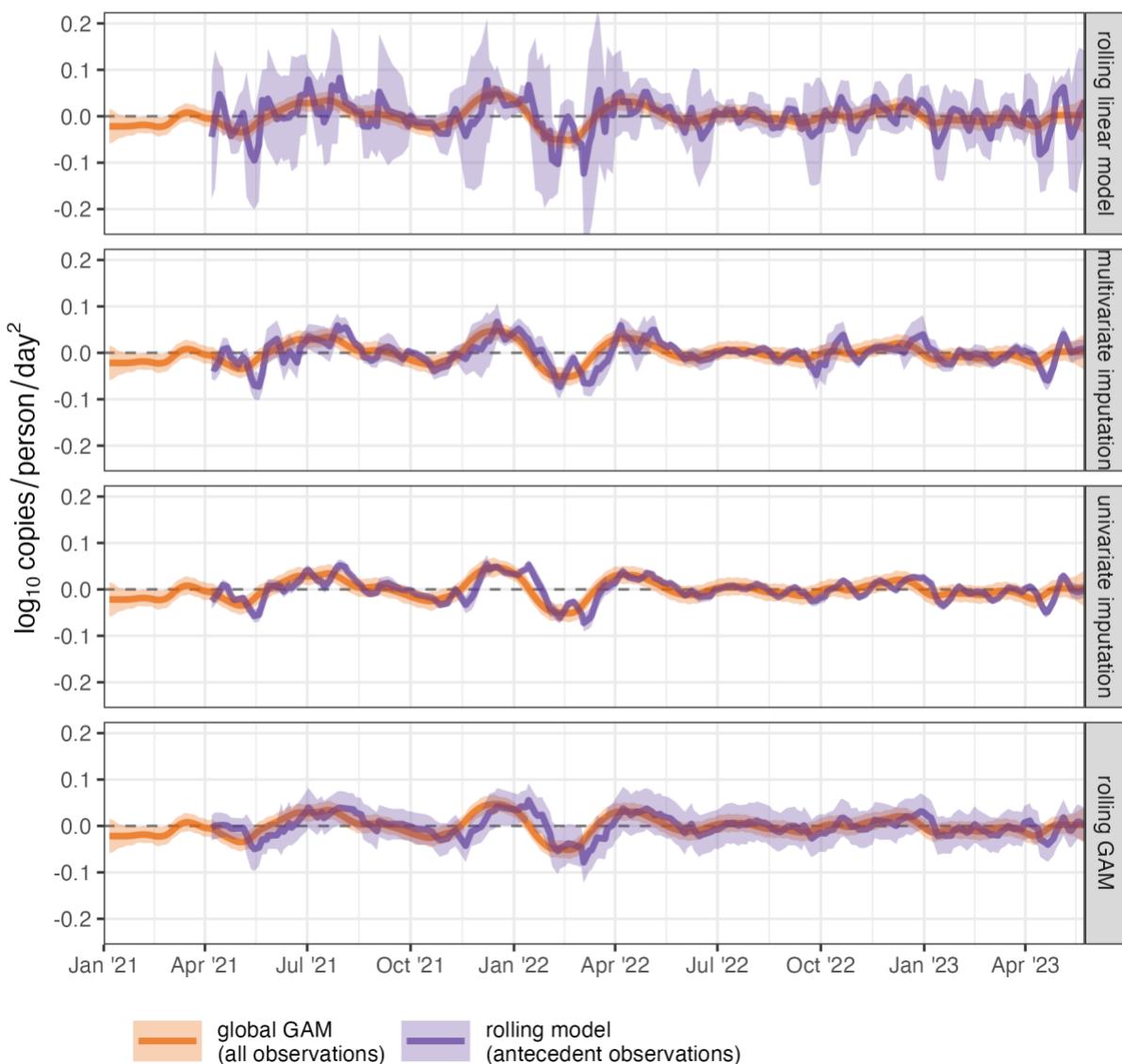
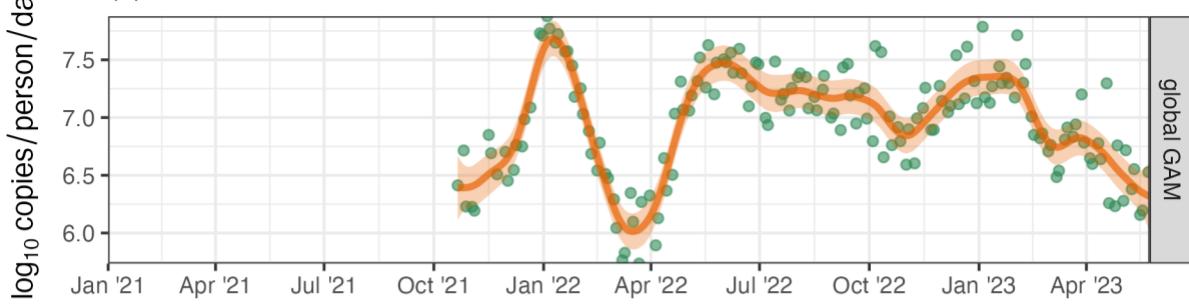


Figure S24. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Raleigh 1 sewershed

## Raleigh 2 Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

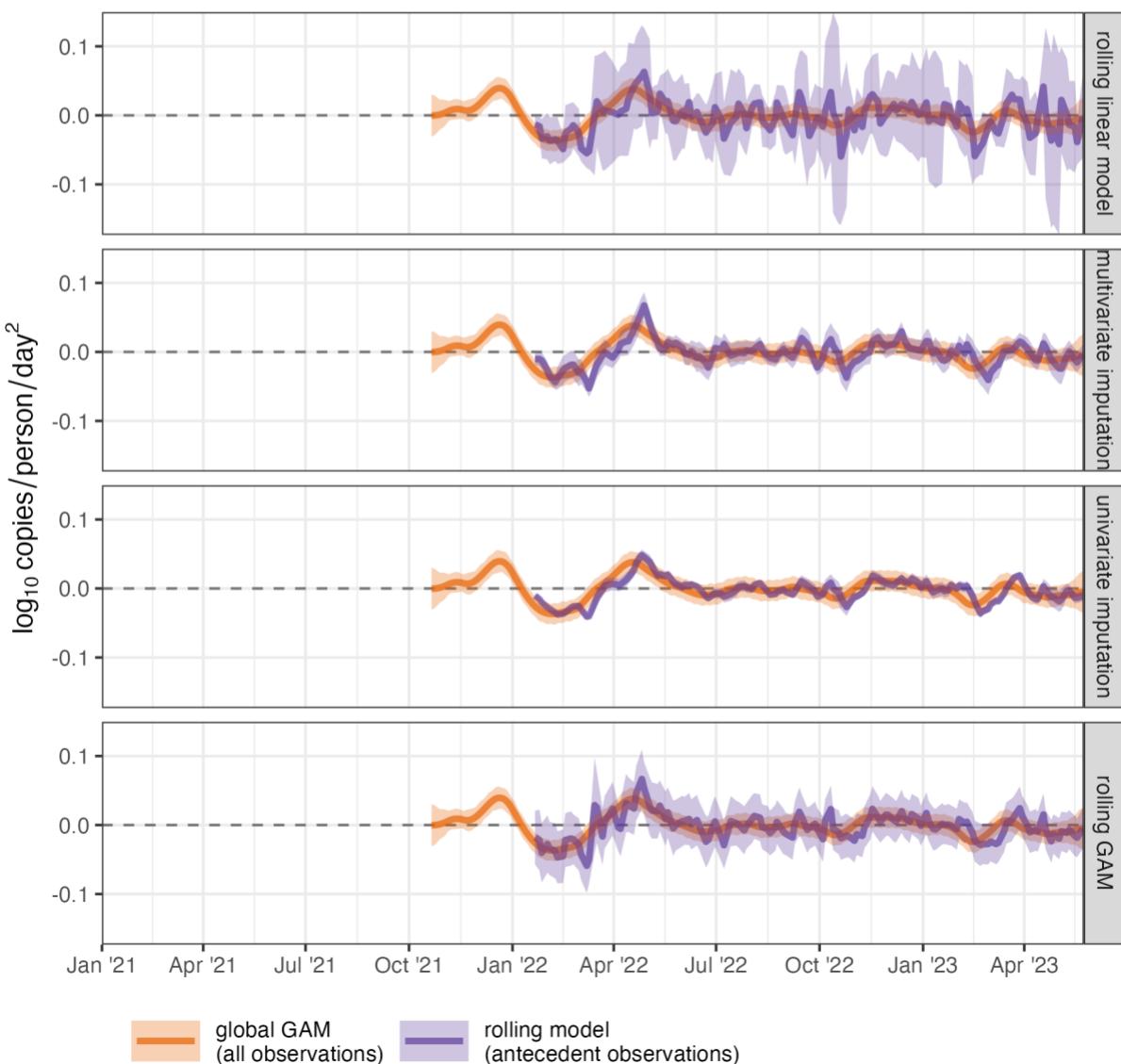
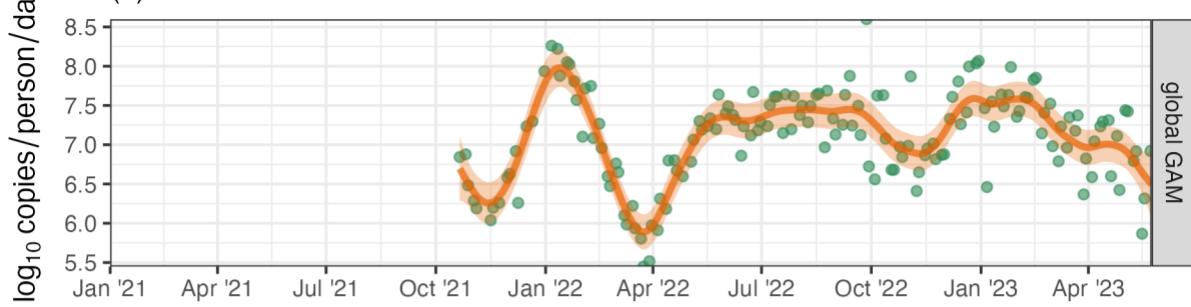


Figure S25. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Raleigh 2 sewershed

## Raleigh 3 Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

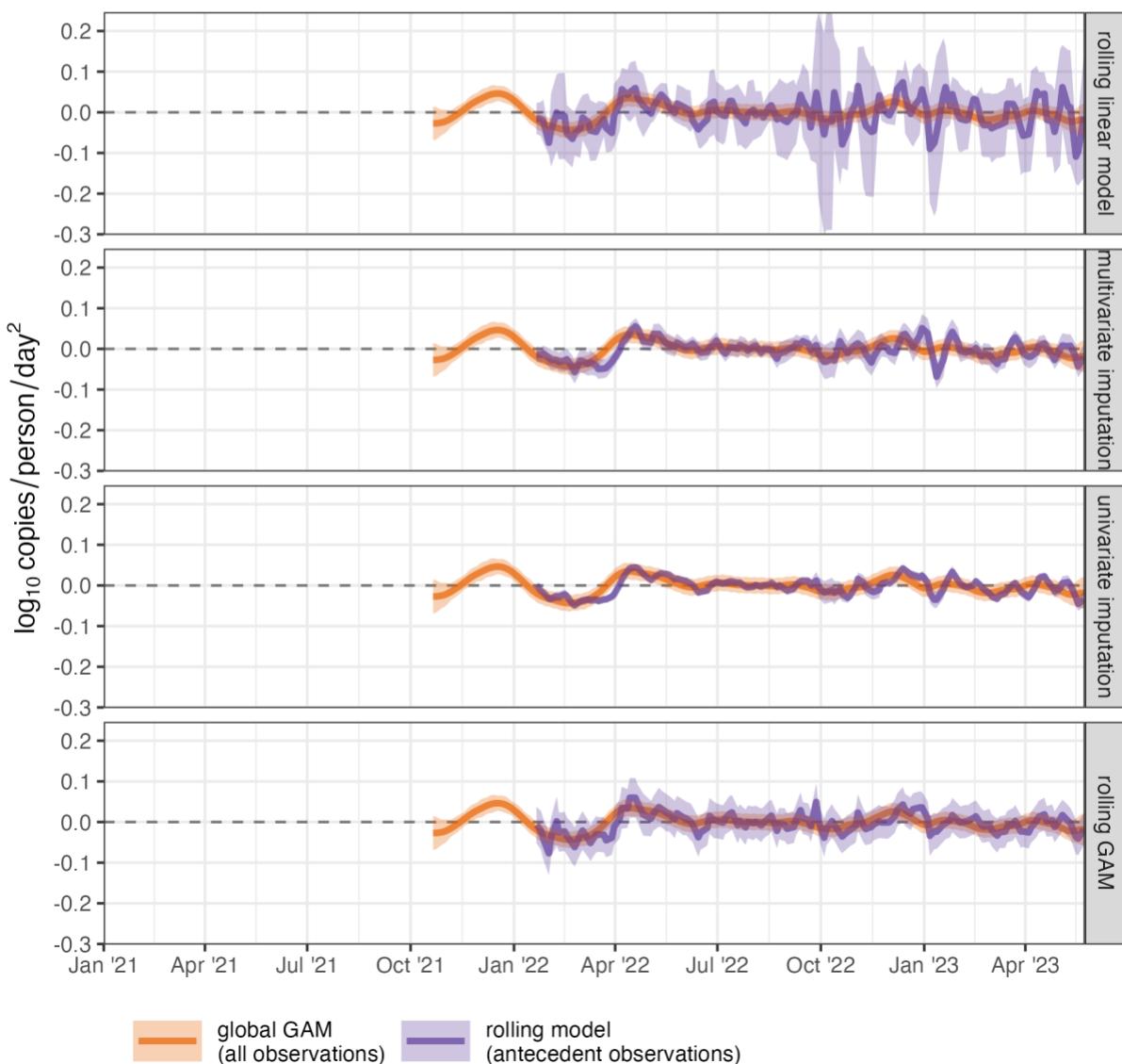
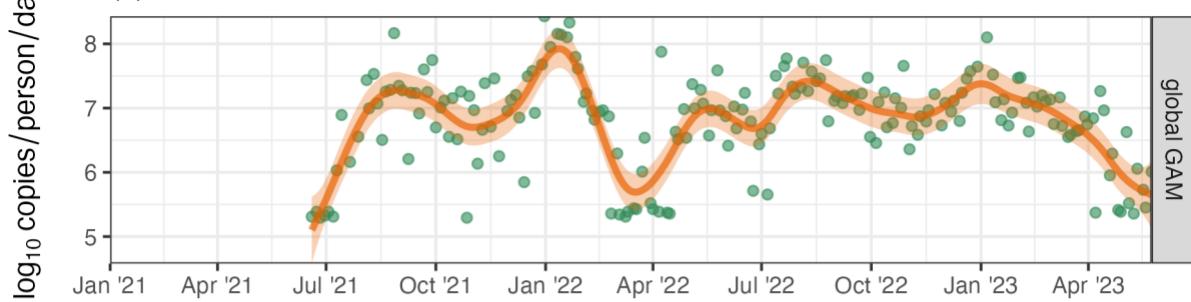


Figure S26. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Raleigh 3 sewershed

## Roanoke Rapids Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

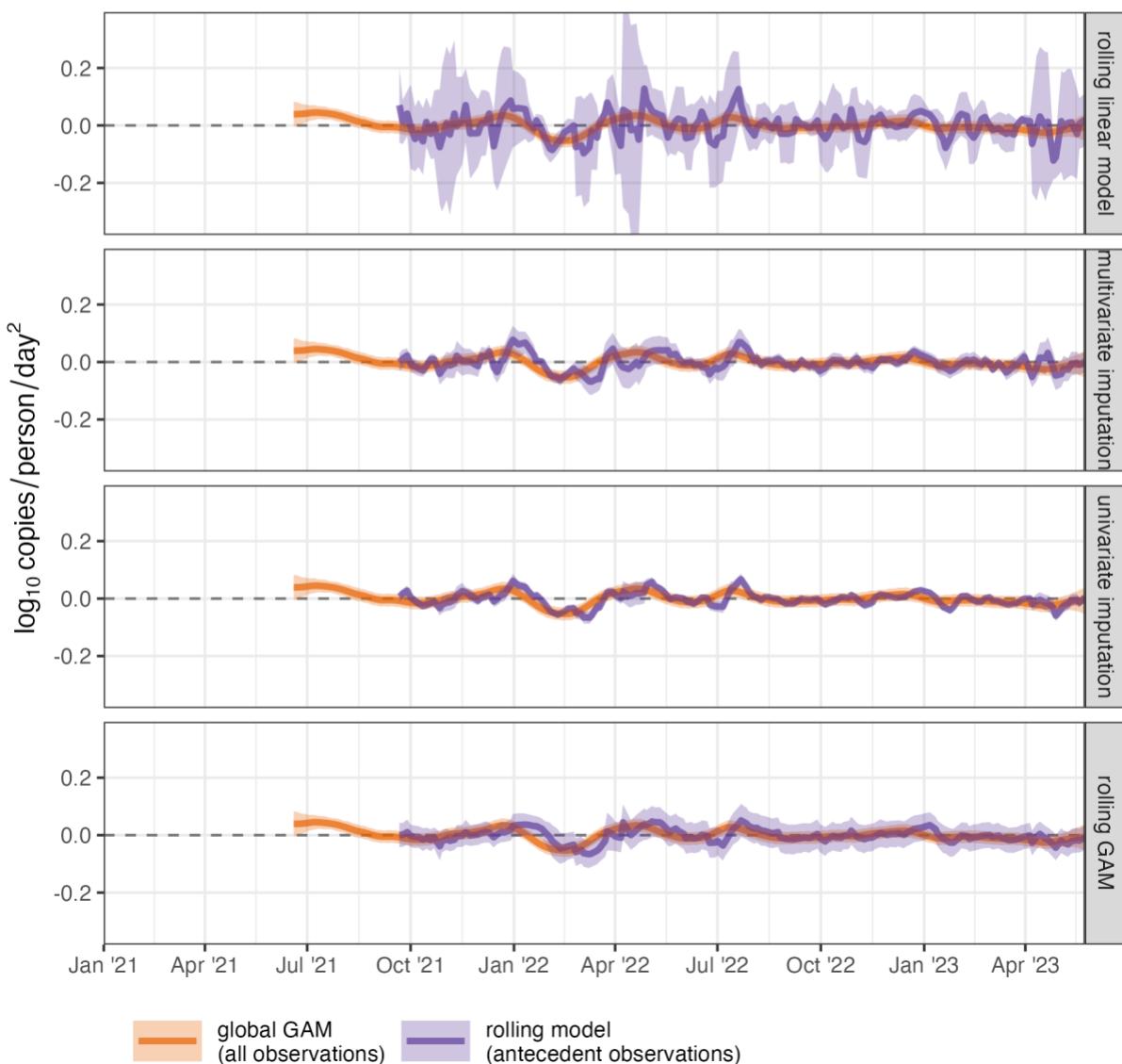
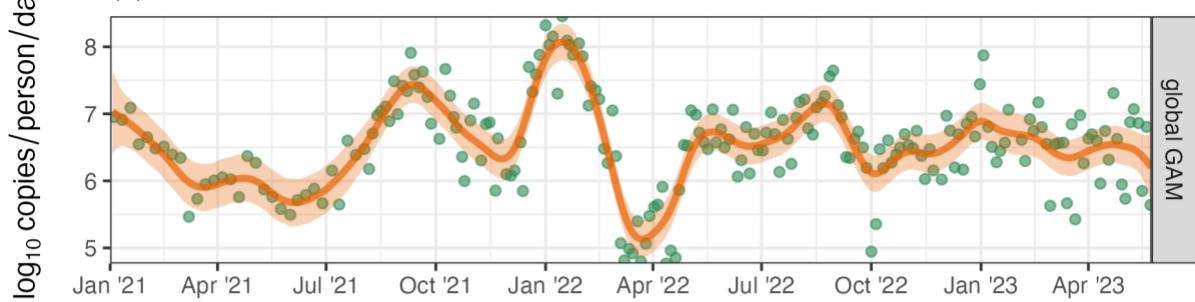


Figure S27. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Roanoke Rapids sewershed

## Tuckaseigee Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

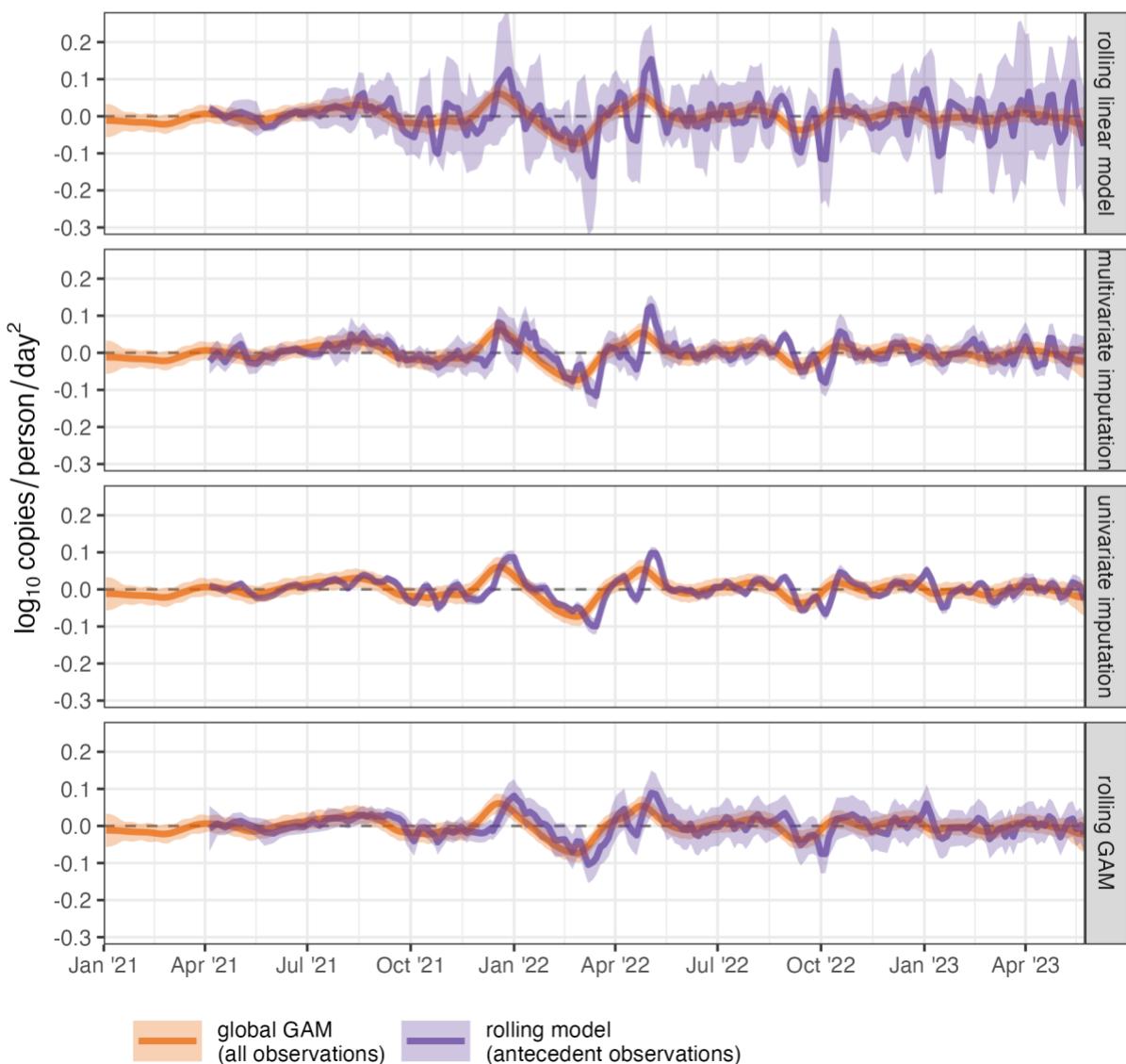
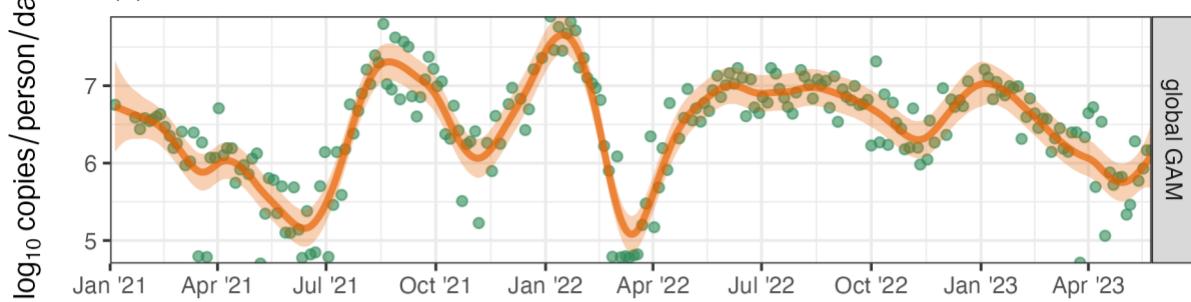


Figure S28. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Tuckaseigee sewershed

## Wilmington Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

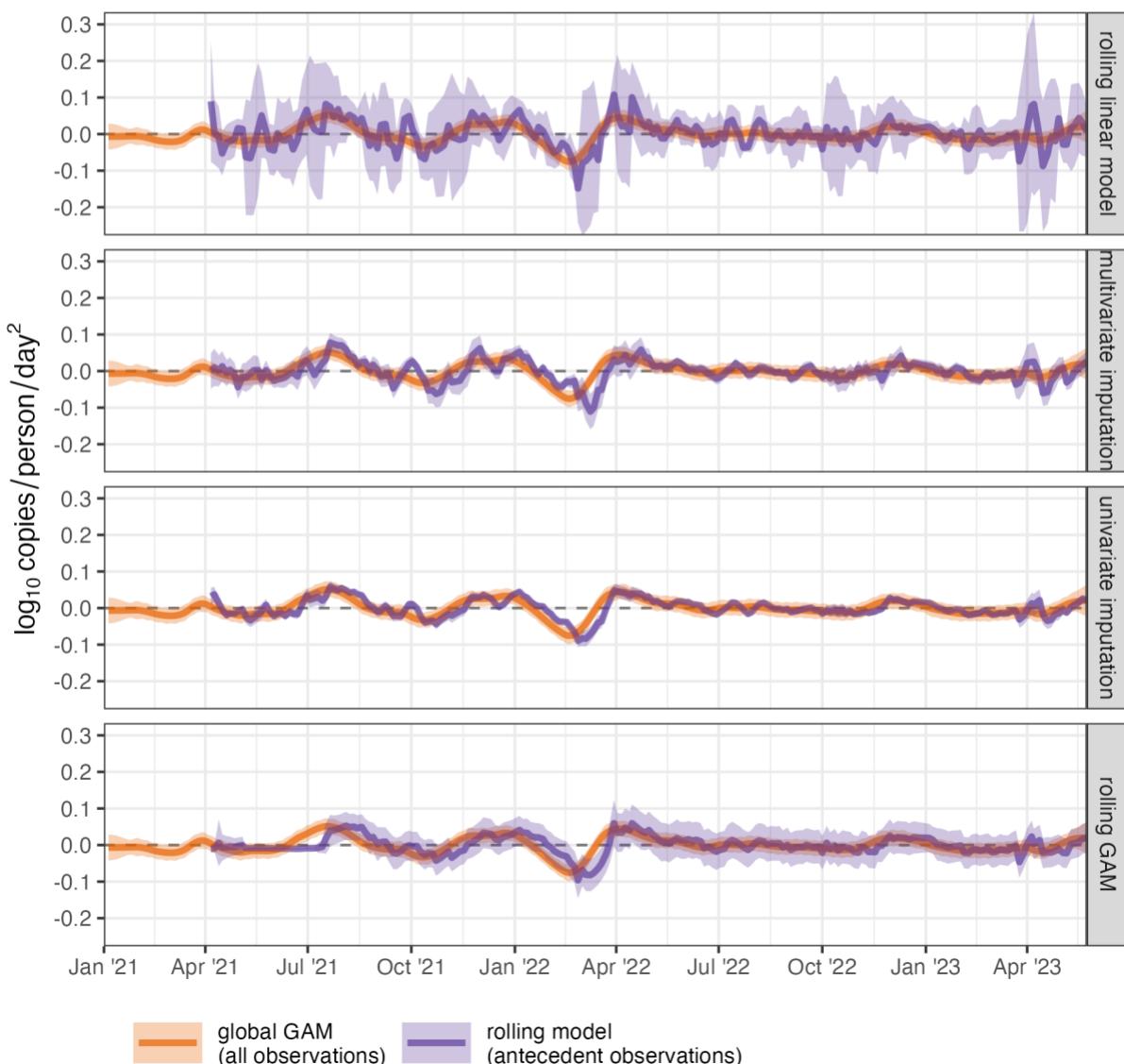
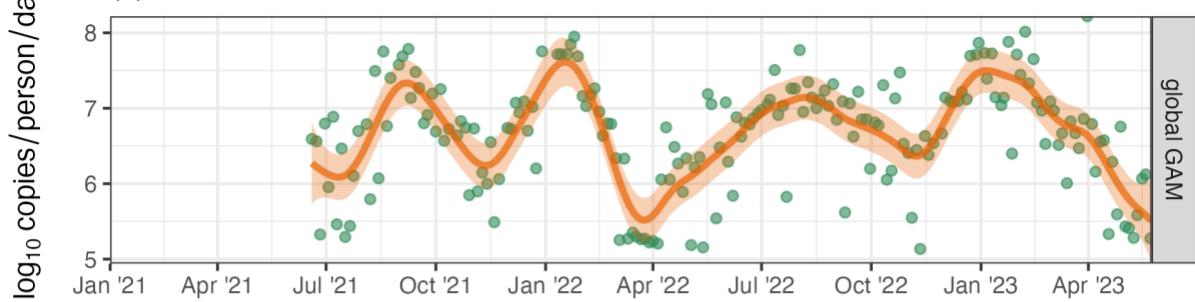


Figure S29. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Wilmington sewershed

## Wilson Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

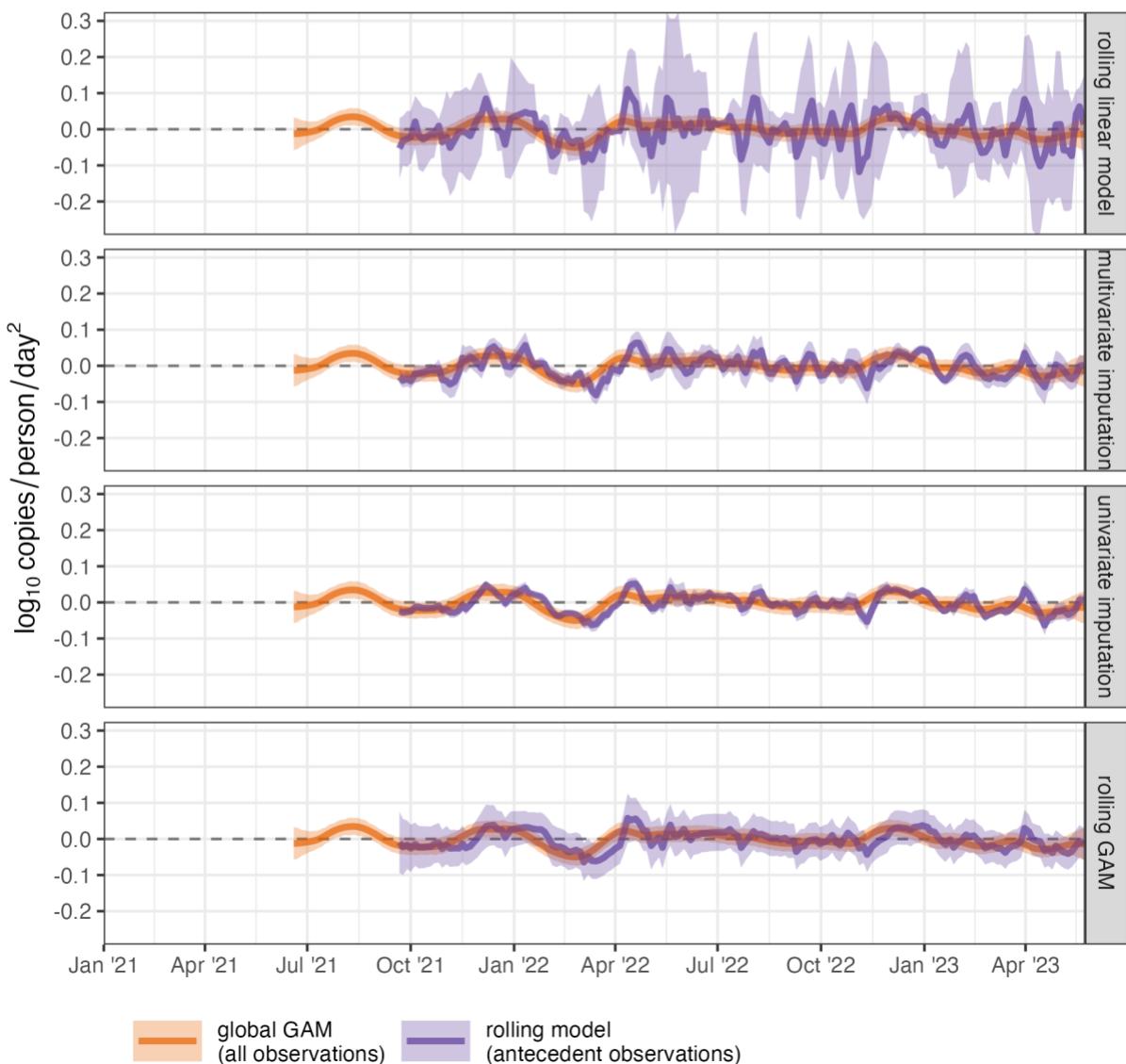
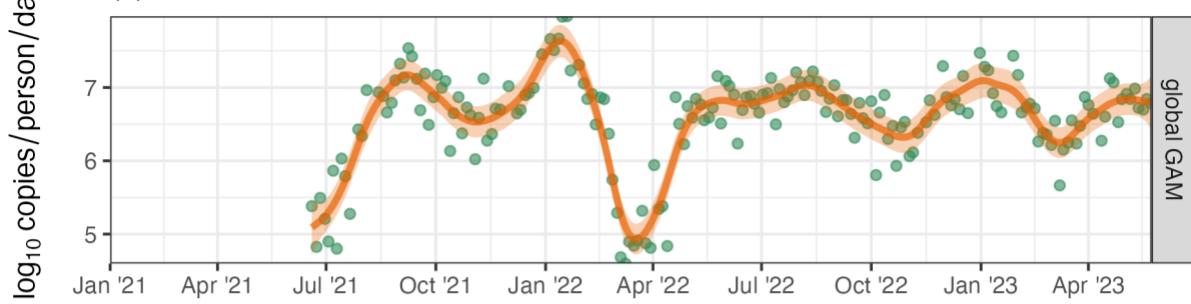


Figure S30. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Wilson sewershed

## Winston-Salem Sewershed

(a) measured viral load and GAM-estimated smooth trend



(b) estimated rate of change

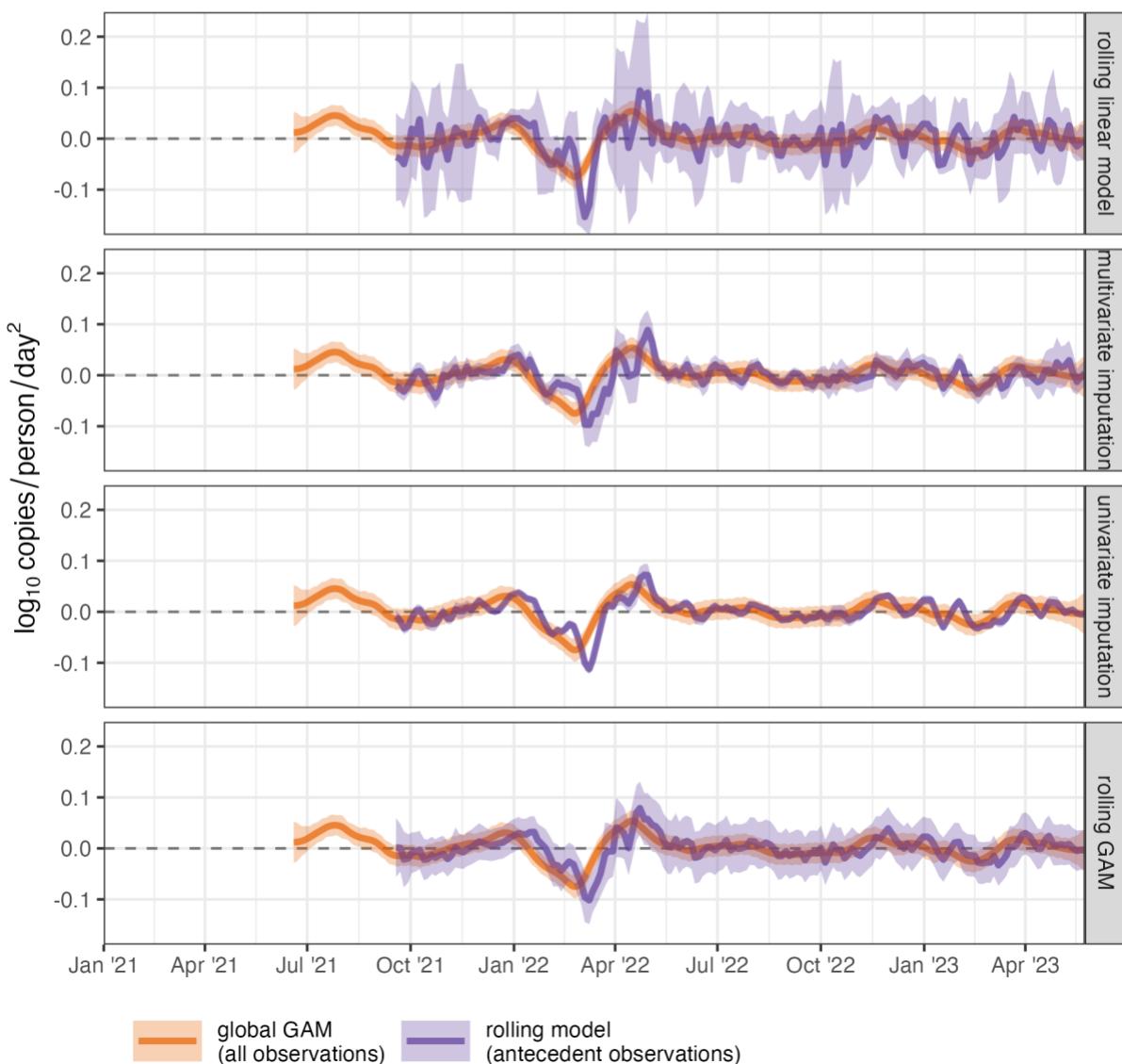


Figure S31. Measured SARS-CoV-2 wastewater per-capita viral load (green points) and estimated mean and 95% CI of the (a) temporal trend and (b) rates of change in the trend for the Winston-Salem sewershed

## S14 Supplementary References

- (1) Simpson, G. L. Modelling Palaeoecological Time Series Using Generalised Additive Models. *Front. Ecol. Evol.* **2018**, *6*, 149. <https://doi.org/10.3389/fevo.2018.00149>.
- (2) Rasmussen, C. E.; Williams, C. K. I. *Gaussian Processes for Machine Learning*; The MIT Press, 2005. <https://doi.org/10.7551/mitpress/3206.001.0001>.
- (3) Betancourt, M. *Robust Gaussian Process Modeling*; Blog Post; 2020. [https://web.archive.org/web/20240320133727/https://betanalpha.github.io/assets/case\\_studies/gaussian\\_processes.html](https://web.archive.org/web/20240320133727/https://betanalpha.github.io/assets/case_studies/gaussian_processes.html).
- (4) Susmann, H. *Derivatives of a Gaussian Process*; Blog post; 2020. <https://web.archive.org/web/20240410015709/http://herbsusmann.com/2020/07/06/gaussian-process-derivatives/>.
- (5) McHutchon, A. J. *Nonlinear Modelling and Control Using Gaussian Processes*; Dissertation; University of Cambridge, 2014. <https://mlg.eng.cam.ac.uk/pub/pdf/Mch14.pdf>.
- (6) Solak, E.; Murray-smith, R.; Leithead, W.; Leith, D.; Rasmussen, C. Derivative Observations in Gaussian Process Models of Dynamic Systems. In *Advances in Neural Information Processing Systems*; MIT Press, 2002; Vol. 15. [https://proceedings.neurips.cc/paper\\_files/paper/2002/file/5b8e4fd39d9786228649a8a8bec4e008-Paper.pdf](https://proceedings.neurips.cc/paper_files/paper/2002/file/5b8e4fd39d9786228649a8a8bec4e008-Paper.pdf).
- (7) Zimmerman, D. L.; Stein, M. Classical Geostatistical Methods. In *Handbook of Spatial Statistics*; Gelfand, A., Diggle, P., Fuentes, M., Guttorp, P., Eds.; CRC Press: Boca Raton, FL, 2010; pp 29–44. <http://www.crcnetbase.com/doi/book/10.1201/9781420072884>.
- (8) Arabzadeh, R.; Grünbacher, D. M.; Insam, H.; Kreuzinger, N.; Markt, R.; Rauch, W. Data Filtering Methods for SARS-CoV-2 Wastewater Surveillance. *Water Sci. Technol.* **2021**, *84* (6), 1324–1339. <https://doi.org/10.2166/wst.2021.343>.
- (9) Schenk, H.; Heidinger, P.; Insam, H.; Kreuzinger, N.; Markt, R.; Nägele, F.; Oberacher, H.; Scheffknecht, C.; Steinlechner, M.; Vogl, G.; Wagner, A. O.; Rauch, W. Prediction of Hospitalisations Based on Wastewater-Based SARS-CoV-2 Epidemiology. *Sci. Total Environ.* **2023**, *873*, 162149. <https://doi.org/10.1016/j.scitotenv.2023.162149>.
- (10) Wood, S. N. *Generalized Additive Models: An Introduction with R*, 2nd ed.; Chapman and Hall/CRC, 2017. <https://doi.org/10.1201/9781315370279>.
- (11) Hopkins, L.; Persse, D.; Caton, K.; Ensor, K.; Schneider, R.; McCall, C.; Stadler, L. B. Citywide Wastewater SARS-CoV-2 Levels Strongly Correlated with Multiple Disease Surveillance Indicators and Outcomes over Three COVID-19 Waves. *Sci. Total Environ.* **2023**, *855*, 158967. <https://doi.org/10.1016/j.scitotenv.2022.158967>.
- (12) Clark, N. J.; Wells, K. Dynamic Generalised Additive Models (DGAMs) for Forecasting Discrete Ecological Time Series. *Methods in Ecology and Evolution* **2023**, *14* (3), 771–784. <https://doi.org/10.1111/2041-210x.13974>.
- (13) Simpson, G. L. *Gratia: Graceful Ggplot-Based Graphics and Other Functions for GAMs Fitted Using Mgcv*; R package version 0.8.1.34; 2023. <https://gavinsimpson.github.io/gratia/>.
- (14) McMahan, C. S.; Self, S.; Rennert, L.; Kalbaugh, C.; Kriebel, D.; Graves, D.; Colby, C.; Deaver, J. A.; Popat, S. C.; Karanfil, T.; Freedman, D. L. COVID-19 Wastewater Epidemiology: A Model to

Estimate Infected Populations. *Lancet Planet. Health* **2021**, 5 (12), e874–e881.  
[https://doi.org/10.1016/s2542-5196\(21\)00230-8](https://doi.org/10.1016/s2542-5196(21)00230-8).

- (15) Soller, J.; Jennings, W.; Schoen, M.; Boehm, A.; Wigginton, K.; Gonzalez, R.; Graham, K. E.; McBride, G.; Kirby, A.; Mattioli, M. Modeling Infection from SARS-CoV-2 Wastewater Concentrations: Promise, Limitations, and Future Directions. *J. Water Health* **2022**, 20 (8), 1197–1211. <https://doi.org/10.2166/wh.2022.094>.
- (16) Al-Faliti, M.; Kotlarz, N.; McCall, C.; Harris, A. R.; Smith, A. L.; Stadler, L. B.; De Los Reyes, F. L.; Delgado Vela, J. Comparing Rates of Change in SARS-CoV-2 Wastewater Load and Clinical Cases in 19 Sewersheds Across Four Major Metropolitan Areas in the United States. *ACS ES&T Water* **2022**, 2 (11), 2233–2242. <https://doi.org/10.1021/acsestwater.2c00106>.