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Bachelor of Science
The Ohio State University
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Thesis Faculty Advisor: Christine Moe, PhD, MS
Thesis Field Advisor: Alicia Kraay, PhD, MPH

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

Mathematical model for SARS-CoV-2 transmission and wastewater dynamics on Emory University campus

By Cassandra Boutelle

Since the start of the SARS-CoV-2 pandemic, wastewater-based epidemiology approaches for surveillance developed rapidly to fill gaps left by traditional clinical surveillance systems. This study aims to quantify how wastewater and infection dynamics changed in response to public health interventions and the emergence of variants. We use an SEIR-like model to simulate COVID-19 dynamics on Emory University campus over the 2020-2021 and 2021-2022 academic years. The model was run over five time periods with distinct viral dynamics and university policies: 1) No vaccination 1, no vaccines + no weekly screening. 2) No vaccination 2, no vaccines + weekly screening. 3) Vaccine rollout, active vaccination rate + weekly screening. 4) Delta, vaccination requirement + Delta variant predominance. 5) Omicron, booster vaccination requirement + Omicron variant predominance. Model parameters were defined using values from literature, except for the reproduction number and duration of infectious period which were calibrated for each time period. Infection dynamics of the model were validated by assessing the percent error between newly infectious individuals and new cases reported by Emory University. The average percent error was 2.9% for no vaccination 1, -3.4% for no vaccination 2, -13.2% for vaccine rollout, -11.8% for Delta, and -11.5% for Omicron. The wastewater dynamics of the model were validated for the first two time periods, when wastewater sampling occurred on campus. Simulated SARS-CoV-2 concentration in wastewater was consistent with swab positivity data for no vaccination 1 and 2. For the latter three periods, SARS-CoV-2 concentration was highest at the beginning of the period and then decreased over time. However, the model predicted that SARS-CoV-2 concentration would largely remain above the limit of detection throughout the time periods. Simulated SARS-CoV-2 concentrations briefly dropped below the limit of detection for the sampling method at the end of the Fall 2021 semester (Delta period). Quantitative assays for wastewater surveillance may be more useful when COVID-19 incidence is moderate or high. In the vaccine rollout and Omicron periods, a peak in predicted virus concentration in wastewater preceded a peak in reported cases by 5-17 days and could be used as an early warning for community incidence.

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1 Introduction

1.1 Background on 2019 SARS-CoV-2 Pandemic

The ongoing SARS-CoV-2 pandemic began with a cluster of cases in China's Hubei province who appeared with fever, cough, and chest discomfort. Most of these cases were epidemiologically traced to a seafood market in downtown Wuhan that sold seafood and other live animals (Hu et al., 2021). The Wuhan Municipal Health Commission notified the World Health Organization (WHO) and the public of this outbreak of unknown cause on December 31, 2019 (Hu et al., 2021). In early January 2020, a novel coronavirus, SARS-CoV-2, was isolated and identified as the cause of the outbreak, and by the end of the month, evidence of human-to-human transmission of the virus was confirmed (Hu et al., 2021). The virus quickly spread throughout China and internationally, and the WHO defined COVID-19, the disease caused by SARS-CoV-2, a pandemic on March 11, 2020 (Hu et al., 2021).

1.2 *Wastewater surveillance for SARS-CoV-2*

Since the start of the SARS-CoV-2 pandemic, the need for an effective surveillance system led to rapid development of wastewater-based surveillance. Due to limited diagnostic testing capacities and high number of asymptomatic infections caused by SARS-CoV-2, traditional monitoring systems likely underestimate the true prevalence of disease, which has made it an ideal candidate for wastewater-based surveillance (Y. Wang et al., 2022).

Wastewater-based epidemiology involves the extraction of biomarkers from wastewater to obtain information about a community's health (Mao et al., 2020). By collecting untreated wastewater samples from points with defined geographic catchment areas, the samples can be analyzed for the presence of a biomarker of interest and the community-level health status can be obtained in near real-time (Mao et al., 2020). This method of surveillance has proven to be a useful tool for providing early warnings of pathogenic viruses such as polio, norovirus, and hepatitis A (Brouwer et al., 2018; Hellmer et al., 2014).

Numerous studies have shown the use of wastewater surveillance for SARS-CoV-2 as an early warning sign for community infections. A study conducted on Emory University's campuses determined that wastewater samples that were positive for SARS-CoV-2 RNA preceded case surges by 1-2 weeks. Wastewater surveillance could be used as an early warning for outbreaks that may occur on campus before cases are confirmed through diagnostic testing results (Y. Wang et al., 2022). Another study in New Haven, Connecticut also showed promise of wastewater surveillance as an early warning sign on a population-level. Positive wastewater samples preceded hospitalizations by 1-4 days and reported test results by 6-8 days in situations where testing capacity was limited and reporting was delayed (Peccia et al., 2020).

Wastewater-based surveillance for SARS-CoV-2 may be an even more useful tool when cases are underreported. As of summer 2022, cases are increasingly likely underreported in clinical surveillance systems due to increasing vaccination coverage offering protection against severe disease and widespread availability of at-home antigen tests (Rader et al., 2022). If severe cases surge again, as they did early in the pandemic, wastewater surveillance might also be especially helpful if existing surveillance infrastructure is unable to keep pace with the need for testing. In these scenarios, information about prevalence of SARS-CoV-2 infections on a community level can supplement those reporting systems already in place to glean a more accurate estimate of infection burden in the community. Moreover, validating the use of wastewater surveillance during periods where both wastewater and reliable case data were available can help maximize the usefulness of wastewater-based surveillance data during periods when cases are underreported.

1.3 SARS-CoV-2 vaccine development and emergence of variants

The development of vaccines to prevent SARS-CoV-2 infection has been a focus of pandemic control strategies, and the United States Food and Drug Administration (FDA) provided emergency use authorization (EUA) of three vaccines beginning in December 2020, with vaccine rollout occurring in early 2021 for the general population. The Pfizer-BioNTech COVID-19 Vaccine was issued EUA on 11 December 2020 with an initial efficacy of 95% (FDA, 2020b). The Moderna COVID-19 Vaccine was issued EUA on 18 December 2020 with an initial efficacy of 94.1% (FDA, 2020a). Both the Pfizer-BioNTech and Moderna vaccines use messenger RNA to trigger an immune response and require two doses for complete vaccination (FDA, 2020a, 2020b). Janssen COVID-19 Vaccine was issued EUA on 27 February 2021 with an initial efficacy of 66-67% for preventing moderate to severe disease and 77-85% for preventing severe disease (FDA, 2021). The Janssen vaccine uses adenovirus type 26 to deliver a piece of the SARS-CoV-2 DNA that triggers an immune response and only requires one dose (FDA, 2021).

Each state developed a COVID-19 Vaccination Plan to ensure efficient and equitable administration of vaccines. The Georgia Department of Public Health (GA DPH) implemented a four-phase approach, beginning with critical populations, including healthcare workers, first responders, those aged 65 years and older, and those living and working in long term care facilities (GADPH, 2022). Phase 2 began on 08 March 2021 with increased availability of vaccines to include additional eligible populations at increased risk for severe illness (GADPH, 2022). In June 2021, vaccines became widely available, and Georgia transitioned to Phase 3 with vaccines available for all those recommended by the CDC (GADPH, 2022). Phase 4 involves recovery and mitigation activities including continued vaccination and accurate documentation of vaccinations and adverse events (GADPH, 2022). As information regarding vaccine waning immunity and efficacy against new SARS-CoV-2 variants unfolded, vaccine recommendations and rollout plans were updated. Starting in August 2021, the CDC recommended fully vaccinated individuals receive a booster dose to increase protection in the face of emerging SARS-CoV-2 variants (Johnson et al., 2022).

Over the course of the pandemic, vaccine performance has been affected by the emergence of SARS-CoV-2 variants that influence how the virus spreads and the severity of the disease. WHO has identified five variants of concern (VOC) over the course of the pandemic, with the first VOCs designated in December 2020 (WHO, 2022). Of these variants, the United States has been most affected by Delta and Omicron variants that emerged in June and December 2021, respectively (Johnson et al., 2022). Studies indicate that vaccinations had less impact on transmission of these variants, whether that is due to reduced vaccine efficacy or increased transmission rates, and that waning immunity from vaccination is a concern (Johnson et al., 2022). Before the emergence of VOCs, unvaccinated individuals were 13.9 times more likely to become infected by SARS-CoV-2 compared to fully vaccinated individuals, but this ratio decreased after the emergence of Delta. Unvaccinated individuals were only 5.1 times more likely to become infected compared to those fully vaccinated at the time of Delta predominance (July to November 2021), which indicates that the vaccines were a less effective intervention against the Delta variant (Johnson et al., 2022). Vaccination was useful in preventing severe outcomes during this time; unvaccinated individuals were 16.4 times more likely to experience a COVID-19-associated death compared to fully vaccinated individuals (Johnson et al., 2022). During this period of Delta predominance, the CDC recommended that vaccinated individuals receive booster doses. With the subsequent emergence of Omicron in December 2021, studies indicated that vaccination was less effective at preventing disease against Omicron (compared to Delta), however a booster dose did provide some added protection (Johnson et al., 2022). Unvaccinated individuals were 2.8 and 4.9 times more likely to become infected compared to those vaccinated without a booster dose and with a booster dose, respectively, during Omicron predominance (Johnson et al., 2022). The development of vaccine rollout and the emergence of variants have greatly affected the transmission dynamics of SARS-CoV-2 and the course of the pandemic.

1.4 Objectives

Wastewater surveillance has been shown to be a useful tool as an early warning for surges of SARS-CoV-2 infections, but with the novel and rapidly changing nature of this pandemic, a modeling approach may be useful to gain insight to new developments. This study aims to quantify how wastewater and infection dynamics changed in response to public health interventions and ongoing variant emergence. We use a transmission model validated for the Emory University campus during the 2020-2021 and 2021-2022 academic years to address this question.

2 Methods

2.1 Mathematical model

This study uses a modified susceptible, exposed, infectious, and recovered (SEIR) model to account for the complexities of SARS-CoV-2 transmission dynamics on a university campus. The model is run over five time periods coinciding with Emory University's calendar for the 2020-2021 and 2021-2022 academic years with distinct factors that impacted SARS-CoV-2 transmission:

1. **No vaccination 1** (Fall 2020) from 24 August 2020 to 22 November 2020, no weekly testing
2. **No vaccination 2** (Spring 2021) from 25 January 2021 to 12 March 2021, required weekly testing
3. **Vaccine rollout** (Spring 2021) from 13 March 2021 to 05 May 2021, required weekly testing
4. **Delta** (Fall 2021) from 25 August 2021 to 01 December 2021, 2-dose vaccination requirement, required weekly testing for unvaccinated
5. **Omicron** (Spring 2022) from 25 January 2022 to 31 March 2022, booster vaccination requirement, required weekly testing for unvaccinated

The time periods and the actions taken by Emory University for surveillance and intervention are summarized in Figure 1. No vaccination 1 had no weekly testing requirements and no vaccination requirement, as the FDA had yet to provide EUA for any vaccine. Spring 2021 required all students to comply with weekly asymptomatic screening test and is simulated in two parts: no vaccination 2 and vaccine rollout. Many Emory University students became eligible to obtain a COVID-19 vaccine in Georgia on 08 March 2021, one week prior to the start of the vaccine rollout period. Fall 2021 saw the predominance of the Delta variant, and Emory University implemented a COVID-19 vaccine requirement for all students on campus and removed the weekly asymptomatic screening test requirement for those fully vaccinated. The Omicron variant was predominant in the spring 2022 semester. Vaccinated Emory students were required to obtain a booster dose, and those that were unvaccinated continued to comply with weekly asymptomatic screening tests.

2.1.1 Model structure

This study modifies the traditional SEIR model to incorporate transmission among vaccinated individuals, different levels of disease severity, isolation of cases, a post-symptomatic period, and dynamics of the environment. Figure 2 depicts the flow diagram of the model, and Equations 1-15 describe the model dynamics.

The susceptible compartment (S) includes those who have not been infected with SARS-CoV-2 and have not received complete vaccination. People from the susceptible population are vaccinated at rate ξ (people/day) and move to the vaccinated compartment (V). From this point, the model continues on two paths denoted with subscripts v and s, for those vaccinated and unvaccinated. Breakthrough cases among vaccinated persons have become an important concern with the emergence of SARS-CoV-2 variants. These individuals become infected at lower rates than unvaccinated persons and experience lower viral loads in the nasal mucosa and decreased severity of disease if infected (Vitiello et al., 2021). Individuals who have already been infected with SARS-CoV-2 may also receive a COVID-19 vaccine, however those individuals are not accounted for in the vaccinated compartment of this model.

Individuals may then migrate to the exposed stage (E_v and E_s compartments). Exposed individuals are those that will become infectious, but do not yet have a high enough viral load to infect others or shed virus into the environment. From the exposed stage, an individual will migrate to one of three infectious stages: mild-moderate illness (I_{v1} and I_{s1} compartments), severe illness (I_{v2} and I_{s2} compartments), and isolated (Q_v and Q_s compartments). These stages encompass the entirety of the time an individual is infectious, even if they are not exhibiting symptoms yet. In each infectious stage, an individual sheds virus into the wastewater environment and is infectious, but only those in the mild-moderate illness compartments contribute to transmission of infection. Emory University's policies required that those showing symptoms (severe illness compartments) and those with positive screening tests (isolated compartments) isolate away from other students for the duration of their infectious period, removing them from campus infection dynamics. Asymptomatic individuals are included among other infected individuals in the mild-moderate illness and isolated compartments because viral loads among symptomatic and asymptomatic patients do not differ, so it is assumed that separate compartments for asymptomatic infection are not necessary (Cevik et al., 2021). Those in the severe illness stage have a rate of death, μ.

At rates specific to the infectious stage, individuals move to the post-symptomatic compartment (P_v and P_s). Illness causes prolonged shedding of SARS-CoV-2 through feces, even after an individual has stopped experiencing symptoms and spreading virus through the air (Cevik et al., 2021). Post-symptomatic individuals shed virus into the wastewater environment, but they do not contribute to campus transmission.

From the post-symptomatic stage, individuals move to the recovered stage (R) and remain there for the duration of the model. These individuals are not involved in campus transmission or shedding to the wastewater environment. Since this model is used for short periods of time, waning immunity is not incorporated, as the average duration of immunity has been shown to be longer than the few-month timescale of our simulations (CDC, 2021).

All infectious and post-symptomatic stages contribute shedding of virus into the wastewater environment (W compartment) at rate ω ($\log_{10}$ genome copies (gc)/capita/day).

Virus in the environment has a natural die-off rate, δ. The wastewater environment does not play a role in transmission, as individuals are not exposed to wastewater on campus, but is useful as a barometer of incidence.

2.1.2 Model parameterization and initialization

Most parameters in the model were obtained from the literature or derived using Equations 16-18, and all parameter values for the five time periods are listed in Table 1. Vaccine effectiveness against infection and severe infection (VE_i and VE_m) varied between time periods according to the predominant SARS-CoV-2 variant and information about waning immunity (Collie et al., 2022). The proportion of cases with mild-moderate disease (m) and the rate of death from severe disease (μ) also varied according to the predominant SARS-CoV-2 variant (Iuliano et al., 2022).

Screening test requirements from Emory University were different for each semester, influencing whether a proportion (q_v and q_s) of mild-moderate cases are moved into the isolated compartment. Weekly screening test requirements were implemented in Spring 2021 for all students, but in Fall 2021 and Spring 2022, only unvaccinated students were required to take weekly screening tests. For the time periods and populations without screening requirements, the proportion (q_v and/or q_s) was set to zero, even though it is likely that individuals with mild-moderate illness would self-isolate on their own terms.

The rate of vaccination (ξ) is a daily per capita rate specific to Georgia and the study's vaccine rollout time period (*us_state_vaccinations*, 2022). Before this time period, vaccines were not widely available to Emory University students. In subsequent time periods, Emory University implemented a COVID-19 vaccine requirement that reached nearly 97% compliance prior to the semester start with few new vaccinations among students during the academic year ("Emory University COVID-19 Dashboard," 2022).

The rate of transition between stages, virus shedding rates, and virus die-off rates in the environment were obtained from the literature and remained consistent across time periods with the exception of the duration of the infectious stage in the Delta time period. These durations (φ_1 and φ_2) were calibrated during model formulation to better fit observed case counts from Emory University.

The transmission rate was also calibrated during model formulation for each time period by adjusting the reproduction number (R). The transmission rate depends on a variety of factors specific to the population of interest including social distancing requirements, mask requirements, restrictions for gatherings, online versus in-person learning, and the predominant SARS-CoV-2 variant. Emory University took precautions to limit on-campus transmission, and requirements, as well as students' attitudes and behaviors, changed frequently across the academic years in this study.

The model simulations were initialized based on case reporting from Emory University. Cases reported within the first seven days of each time period were initialized in the exposed stage. For those time periods with vaccination, Equations 19-20 used the proportion of the population that was vaccinated and the vaccine efficacy against infection to divide the group among the vaccinated and unvaccinated populations. The infectious stages were initialized based on cases reported from the eight days prior to the time period. Emory University required screening tests for students at the start of every semester, so we assume there are initially only cases in the isolated and severe illness compartments. The post-symptomatic stage is initialized with cases reported between eight and 26 days prior to the time period. Cases reported by Emory University more than 26 days, but less than three months before the start of the time period, were initialized to the recovered stage. Since many students were away from campus prior to the period start dates, additional individuals were initialized in the recovered compartment based on national case rates for the months prior to the period start (*us_state_vaccinations*, 2022).

The susceptible and vaccinated compartments were initialized based on Emory University counts of the number of students participating in on-campus classes for each semester and the percent of students vaccinated ("Emory University COVID-19 Dashboard," 2022). For the no vaccination 1, no vaccination 2, and vaccine rollout periods, only first-year undergraduates and an estimated half of graduate students attended on-campus classes, but all students returned to on-campus classes for the Delta and Omicron periods. The wastewater compartment was initialized by adding the number of individuals initialized in the infectious and post-infectious stages and multiplying that value by the virus shedding rate (ω) and the rate of virus die-off ($1/\delta$), except in the vaccine rollout period. Since the vaccine rollout period begins immediately after the spring 2021 no vaccination period, the wastewater compartment is initialized with using the amount in the wastewater compartment from the last timestep of the no vaccination period. Initial conditions for each time period are shown in Table 2.

2.2 Model validation

To ensure the model simulates reasonable dynamics, the model was validated using case reporting data and wastewater sample data from Emory University. Case reporting data were collected for Emory University's COVID-19 Dashboard where every positive case reported to the university was deidentified and published publicly, indicating the case report date and whether the case was a student or staff/faculty member ("Emory University COVID-19 Dashboard," 2022). Due to the relatively small size of the student population and limited testing capacity on weekends, daily case counts fluctuated over the time periods, so the weekly rolling average of reported cases was used to assess the model-simulated case counts. The weekly percent error was calculated for each model timestep using the rolling average of reported case counts and rolling average of simulated cases, accounting for a two-day lag in case reporting. The average percent error was calculated to assess the overall fit of the model.

Wastewater samples were collected from manholes connected to residence halls on Emory University's campuses on a weekly basis from 24 August 2020 to 12 March 2021 (Y. Wang et al., 2022), during both no vaccine periods. Wastewater data were not available during any of the three vaccine periods. The collected Moore swabs were processed and analyzed using skimmed milk flocculation, RNA extraction, and real-time quantitative reverse-transcription polymerase chain reaction (RT-qPCR) to yield a positive or negative result for the presence of SARS-CoV-2 RNA (Liu et al., 2022). The limit of detection (LOD) for the Moore swabs used was 0.7 $\log_{10}$ genome copies (gc)/mL (Liu et al., 2022). An average of seven swabs were collected from manholes around Emory University campus each sampling day, with a minimum of 2 swabs collected on 24 August 2020 and a maximum of 16 swabs collected on 15 March 2021. The percent of swabs with positive results for the presence of SARS-CoV-2 RNA increased over the study period from 0% (0 positive swabs) in August 2020 to 66% (25 positive swabs) in March 2021. Over the entire period, an average of 23% of swabs were positive each sampling day. The data are more completely described in Figure 3. The model estimated the amount ($\log_{10}$ gc) of virus present in the wastewater environment at each timestep, and the estimated concentration of SARS-CoV-2 in the wastewater was calculated from the amount given by the model and the estimated volume of a sampling area. The volume of a sampling area was estimated based on expected concentrations for the no vaccine 1 and no vaccine 2 time periods, when wastewater samples were taken. For the Delta and Omicron time periods, the sampling area volume increased in proportion with the increase of the on-campus student population. For the time periods when campus wastewater was tested (no vaccination 1 and 2), the simulated wastewater environment was validated by calculating the concentration of SARS-CoV-2 in the wastewater environment, comparing it to the LOD for Moore swabs, and assessing if higher concentrations align with the days when positive samples were detected.

2.3 *Model analysis*

This model was used to simulate the spread of SARS-CoV-2 in the population and shedding into the wastewater environment across the five time periods previously defined.

The main distinctions between these periods were level of vaccination in the population, the efficacy of vaccination, and the dynamics of the different variants. In the first two models, no vaccination 1 and 2, vaccination was not present in the population, and no VOC had emerged yet. Additionally, both wastewater and case data were available for these two periods. In the period of vaccine rollout, vaccine efficacy was high and prevented many infections, but few students were vaccinated. With the emergence of Delta and subsequently Omicron, most students were vaccinated, however the success of vaccination as a prevention measure was slightly, and then greatly, reduced.

While case data were available during the three vaccine periods, wastewater samples were not available. For the first two time periods, model results were calibrated such that model simulations were consistent with both reported cases and viral RNA concentrations in wastewater. For the last three time periods in which vaccination was available (but different variants were circulating), the model was calibrated to be consistent with case data only, with changes in wastewater dynamics being simulated. These model simulations can provide insight into how the variations in vaccination level, vaccine efficacy, and SARS-CoV-2 variant influence the wastewater environment and may affect wastewater surveillance.

3 Results

3.1 Model validation results

All models' transmission dynamics were validated using case reporting data from Emory University. In addition, the wastewater dynamics, the changes in levels of SARS-CoV-2 in the wastewater environment, for the periods no vaccination 1 and no vaccination 2 were validated using data collected from wastewater samples collected by Emory University.

3.1.1 Validation of transmission dynamics

Model structures and parameters were validated by comparing observed cases reported from Emory University and the expected case counts simulated by the models. The number of cases simulated by each model are plotted with the daily cases and rolling weekly average of cases reported by Emory University in Figure 4. Simulated case counts are the total number of individuals moving from the exposed stage to the infectious stage on each day. The simulated cases generally follow the basic shape of cases reported from Emory University.

To analytically assess the fit of the model to reported case numbers, the weekly percent errors were calculated over each time period using the weekly rolling averages of reported and simulated cases and are plotted in Figure 5. Most percent errors stayed within 100%, however there are two notable exceptions. In the middle of the no vaccinated 2 period, a spike in reported cases was not captured by the model. Also, in the Delta period, simulated cases did not capture a surge in reported cases in the last week of the time period. Overall, the model simulated case numbers above and below what was expected from reported cases somewhat equally. The average percent error was calculated to assess the overall fit of the model: 2.9% for no vaccination 1, -3.4% for no vaccination 2, -13.2% for vaccine rollout, -11.8% for Delta, and -11.5% for Omicron.

3.1.2 Validation of wastewater dynamics

The concentration of $\log_{10}$ gc SARS-CoV-2 per mL in the wastewater environment was estimated using an estimate of the volume of wastewater in a sampling area. Panels A and B of Figure 6 show the simulated concentration of SARS-CoV-2 in the wastewater environment with the number of positive and negative swabs collected on each sampling day. Wastewater samples were only collected during the no vaccination periods. Overall, when the simulated concentration of SARS-CoV-2 exceeded the LOD, positive samples were expected, and the number of positive samples increased as the concentration of SARS-CoV-2 in the environment increased.

3.2 Model simulation and prediction results

The dynamics from each model are described in Table 3. The average number of cases per day was 3.0 for no vaccination 1, 10.6 for no vaccination 2, 2.9 for vaccine rollout, 4.2 for Delta, and 7.5 for Omicron. The estimated average concentration of SARS-CoV-2 in the wastewater environment was 1.1 $\log_{10}$ gc/mL for no vaccination 1, 3.8 $\log_{10}$ gc/mL for no vaccination 2, 3.2 $\log_{10}$ gc/mL for vaccine rollout, 0.8 $\log_{10}$ gc/mL for Delta, and 2.5 $\log_{10}$ gc/mL for Omicron. The estimated concentration was above the LOD 45% of the time for no vaccination 1, and 55% of the time for Delta. For no vaccination 2, vaccine rollout, and Omicron, the estimated concentration was always above the LOD.

While the wastewater dynamics for the no vaccination 1 and no vaccination 2 time periods were validated using wastewater surveillance data from Emory University, the other time periods are predictions of the wastewater dynamics. The predicted wastewater environment concentrations from the vaccine rollout, Delta, and Omicron time periods are shown in Figure 6. For each of these time periods, the predicted concentration of SARS-CoV-2 in the wastewater increased at the beginning of the time period and then decreased over time. The vaccine rollout and Omicron periods never experienced SARS-CoV-2 concentration in wastewater below the LOD. For Delta, however, after an initial increase, the concentration fell below the LOD for the last month of the time period.

The wastewater reached a maximum estimated concentration of 6.1 $\log_{10}$ gc/mL on 15 March 2021 in the vaccine rollout period. This peak preceded the peak case count for the period, 16 cases on 20 March 2021, by 5 days. For the Omicron period, the estimated SARS-CoV-2 concentration in wastewater peaked at 4.6 $\log_{10}$ gc/mL on 15 January 2022, 17 days before the peak case count of 27 on 01 February 2022. A peak in virus concentration in wastewater did not precede the peak in cases for the Delta period. SARS-CoV-2 concentration in wastewater peaked at 1.6 $\log_{10}$ gc/mL on 11 September 2021, while cases peaked at 51 cases on 02 September 2021.

4 Discussion

4.1 Validation

The number of cases simulated by the model aligned well with reported cases from Emory University overall. For the no vaccination 1 period, both simulated and observed cases increased gradually over time. The no vaccination 2 period had a spike of cases in late February 2021 that the model did not capture. However, simulated cases increased from the start of the time period. It is unclear what may have caused the observed spike in cases, but the increase begins after Presidents' Day weekend. While Emory University students did not have the day off from classes, it is possible that transmission in Atlanta increased overall since others were traveling or being social over the long weekend. Over the vaccine rollout period, both the model and case reporting showed a generally decreasing trend in cases over time. As students returned to campus for the semester at the start of the Delta period in August 2021, cases were initially very high, but decreased quickly and remained lower over the course of the semester as seen in both the model and case reporting. The sharp increase of the percent error in the last week of the Delta period is likely explained by an increase in reported cases as students returned to campus after traveling for Thanksgiving. Since the model did not incorporate time-varying parameters, changes in transmission dynamics like this in the middle of a model period were not captured. The Omicron period experienced a similar trend in cases reported that is captured by the model. While Delta and Omicron variants led to case surges across the country, cases on campus stayed relatively low likely due to policies put in place by Emory University including mask requirements for everyone on campus and restricting in-person activities outside of classes.

The concentration of SARS-CoV-2 in the wastewater environment simulated by the model aligns well with the number of positive swabs sampled from Emory University manholes. Since the model failed to simulate the spike in cases in late February 2021 of the no vaccination 2 period, the simulated concentration also failed to align with the increase of positive swabs in early February 2021. When the concentration reached above the LOD of the Moore swabs that were used for sampling, more positive samples were collected, and as the concentration increased, so did the number of positive samples tested. This indicates that the wastewater dynamics are a reasonable simulation for what actually occurred in the wastewater during both no vaccine periods.

4.2 Simulation and Prediction

The two periods with the most similar parameters and university policies were no vaccination 1 and 2. Although no vaccination 1 was run nearly twice as long as no vaccination 2, the R for no vaccination 2 was much higher, leading to higher case counts over the course of the simulation period. With the vaccine rollout period, R was lower, and some students began to gain protection through vaccination, resulting in lower case counts. In the 2021-2022 academic year, more students were on campus, and this was included as a part of model dynamics. Comparing the Delta and Omicron simulations, even though R was much higher for the Delta period, there were fewer cases than in the Omicron period, due to higher vaccine efficacy against the Delta variant compared to the Omicron variant as well as higher infectivity of the Omicron compared with the Delta variant.

The prediction of the SARS-CoV-2 concentration in wastewater can be useful to hypothesize what wastewater surveillance may have looked like during these time periods. For the vaccine rollout and Omicron simulation periods, the estimated concentration never falls below the Moore swab LOD and indicates a peak in the first week. One would expect to have detected positive samples throughout this time period, with a higher number of positive samples in the first month. The estimated SARS-CoV-2 concentration in wastewater around the Delta time period ending in December 2021 was below the LOD. When the estimated virus concentration is below the LOD, some positive wastewater samples may still have been observed, but the number of positive samples would be lower than during the months of September and October 2021, when the estimated concentration of virus in the wastewater was higher. Quantitative assays measuring concentration of SARS-CoV-2 RNA in wastewater may provide more useful information than positive/negative swabs when COVID-19 incidence is moderate or high.

As observed in the vaccine rollout and Omicron periods, predicted wastewater concentration peaked 5 and 17 days before the peak in reported cases. Since the concentration of the wastewater was always above the LOD in these periods, one would expect to have detected mostly positive swabs. However, if quantitative assays were used in wastewater surveillance, the increase in SARS-CoV-2 concentration could be used as an early warning sign for an increase in cases. Even in the case of the Delta period where the concentration peak did not precede the peak in cases, the curves align somewhat. The predicted SARS-CoV-2 concentration in wastewater increases at the beginning of the period along with the number of cases reported. In instances with high incidence and limited testing capacity or low levels of case reporting, an observed increase in SARS-CoV-2 concentration in wastewater could still provide useful insight into the level of infection in a community.

The results from the simulations and predictions of this model align well with other studies looking at wastewater-based SARS-CoV-2 surveillance methods overall. Studies from other universities also indicated that the concentration of virus in wastewater could be used as an early signal for cases in campus buildings (Betancourt et al., 2020; Gibas et al., 2021; Scott et al., 2021). Some studies also showed that wastewater surveillance could detect as few as one asymptomatic case in a residence hall (Gibas et al., 2021). Another Emory University study showed that as few as 1-4 cases in a building were detected by Moore swab samples 71.4% of the time (Liu et al., 2022). However, the estimated concentration from the model in our study suggests that the Moore swab method of sampling may not be sufficient to detect just one case. Virus concentration in the wastewater when case numbers are very low, like the end of the

Delta period, may not be high enough to return an increased number of positive samples. This highlights the added usefulness of quantitative assays that measure virus concentration. The difference in results of these Emory University studies may be due to limitations in estimating the simulated virus concentration in wastewater for our model, which are further explained in the limitations section.

4.3 Limitations

There are several limitations to this study. As with any model, the produced transmission and wastewater dynamics cannot perfectly simulate what truly occurred during these time periods, but these simulations can be helpful. Due to time constraints, the only parameters calibrated for each model were the R and infectious stage duration. Formal fitting of more model parameters, particularly period specific shedding rates, may have a produced models that more accurately simulate transmission and SARS-CoV-2 concentration in wastewater on campus. The shedding rate is one of the most uncertain parameters in the model, as there is limited literature looking into differences in shedding rates for the different variants, and our wastewater data was limited to the first two time periods, before VOCs emerged in the United States. Since the shedding rate is a key parameter to the simulation of the SARS-CoV-2 concentration in wastewater, it would have been useful to calibrate this parameter. Additionally, the validation of the wastewater dynamics was limited due to the type of wastewater surveillance data available. The model simulates the amount of SARS-CoV-2 present in the wastewater environment as a whole, while each swab from the surveillance data gives information about the presence of SARS-CoV-2 RNA above the LOD concentration at one specific collection site. The volume to calculate the virus concentration in wastewater simulated by the model was estimated based on the expected concentration to reach the LOD during the time periods when wastewater data were available. Due to the difference in scale, only broad conclusions that the trend of virus concentration in wastewater seemed reasonable could be drawn. This model also has limited use for settings outside of Emory University. The model structure and parameters were specifically designed to capture the policies and actions taken by Emory University over the 2020-2021 and 2021-2022 academic years.

5 Conclusion

This model effectively reproduced viral transmission and wastewater dynamics across the 2020-2021 and 2021-2022 academic years at Emory University. Emory University could use information from this model to better understand what they would expect to observe if they were to continue SARS-CoV-2 surveillance through wastewater sampling. It could also be useful in predicting viral transmission dynamics in the campus population for future semesters. While this model is specifically tailored to Emory University's policies, other medium-sized universities may be able to use this model as a base and make adjustments to align with the actions their administration implemented over the course of the pandemic.

Figures, Tables, and Equations

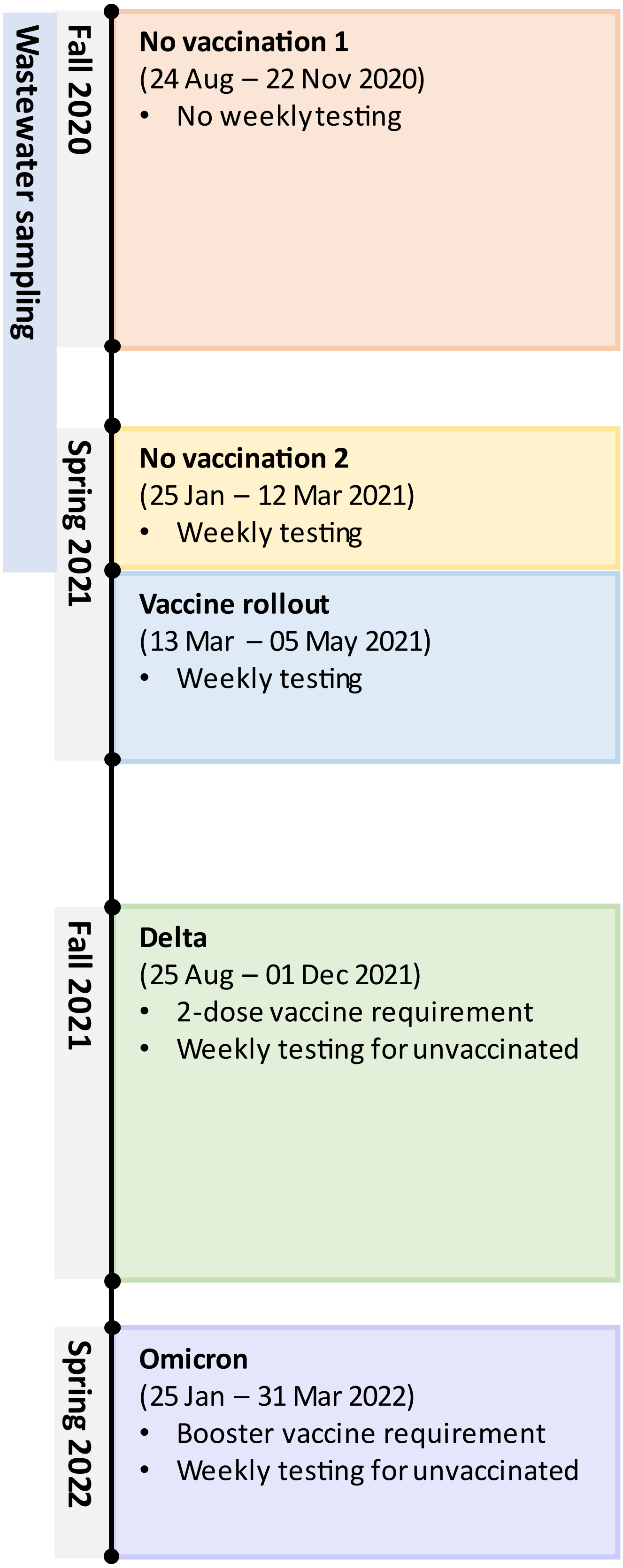

Figure 1: Timeline of simulated time periods with the relevant university requirements for vaccination and testing.

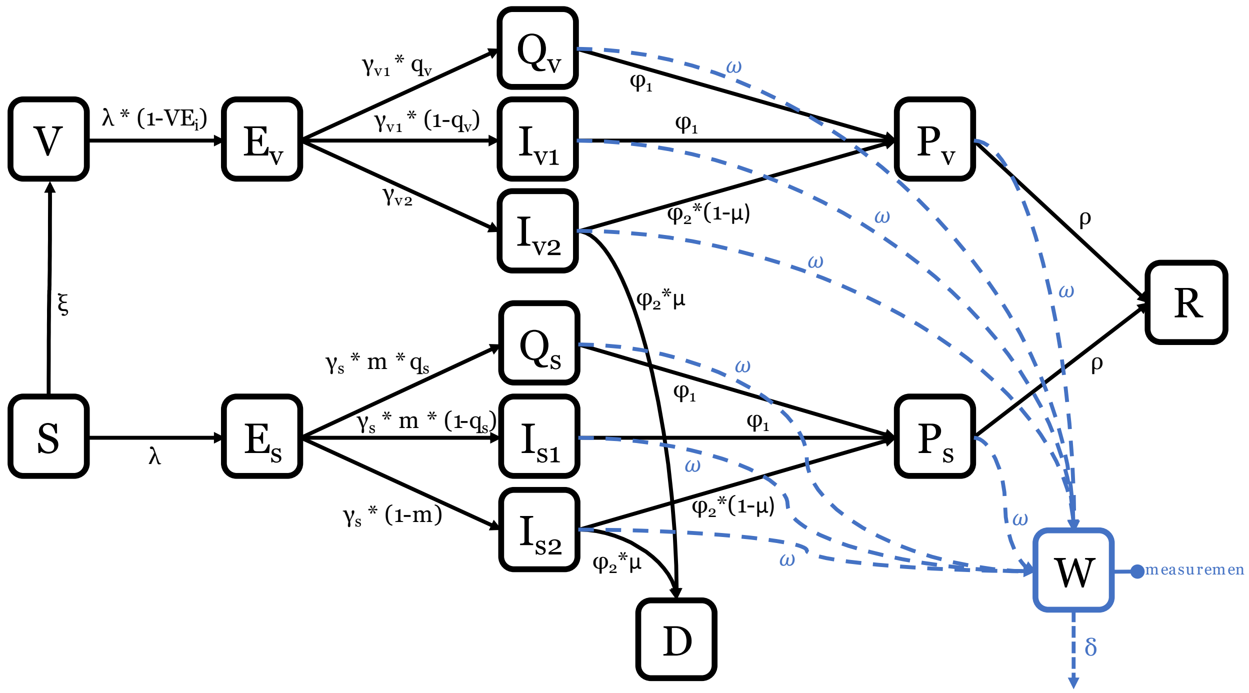

Figure 2: Model flow diagram. Individuals may begin in the susceptible (S) or vaccinated (V) compartment. For those time periods where active vaccination occurred, individuals move at the per capita rate of ξ from susceptible to vaccinated. From those compartments, individuals may move to the exposed stage (E_v and E_s) at the rate λ per day, accounting for vaccine efficacy against illness (VE_i) where appropriate. From the exposed stage, individuals will move to the infectious stage and be placed into one of three compartments: isolated (Q_v and Q_s), mild-moderate illness (I_{v1} and I_{s1}), or severe illness (I_{v2} and I_{s2}). Individuals move at rate γ and are sorted into the different compartments according to rate of severe disease (m) and sensitivity of screening testing (q). Individuals in the severe compartments have a death rate of μ. After the infectious stage, individuals move to the post-symptomatic stage (P_v and P_s) at rate φ. All individuals in the infectious and post-symptomatic stages shed virus into the wastewater environment (W) at rate ω, but only those in the infectious stage contribute to population transmission dynamics. Individuals then move to the recovered stage (R) at rate ρ and remain there for the duration of the model. Virus in the wastewater environment dies-off at the rate δ.

The model dynamics are described by the following equations:

$$\frac{dS}{dt} = -\lambda * S - \xi * S \quad [1]$$

$$\frac{dV}{dt} = \xi * S - \lambda * (1 - VE_i) * V \quad [2]$$

$$\frac{dE_v}{dt} = \lambda * (1 - VE_i) * V - (\gamma_{v1} + \gamma_{v2}) * E_v \quad [3]$$

$$\frac{dE_s}{dt} = \lambda * S - \gamma_s * E_s \quad [4]$$

$$\frac{dQ_v}{dt} = \gamma_{v1} * q_v * E_v - \varphi_1 * Q_v \quad [5]$$

$$\frac{dI_{v1}}{dt} = \gamma_{v1} * (1 - q_v) * E_v - \varphi_1 * I_{v1} \quad [6]$$

$$\frac{dI_{v2}}{dt} = \gamma_{v2} * E_v - \varphi_2 * I_{v2} \quad [7]$$

$$\frac{dQ_s}{dt} = \gamma_s * q_s * m * E_s - \varphi_1 * Q_s \quad [8]$$

$$\frac{dI_{s1}}{dt} = \gamma_s * (1 - q_s) * m * E_s - \varphi_1 * I_{s1} \quad [9]$$

$$\frac{dI_{s2}}{dt} = \gamma_s * (1 - m) * E_s - \varphi_2 * I_{s2} \quad [10]$$

$$\frac{dP_v}{dt} = \varphi_1 * (I_{v1} + Q_v) + \varphi_2 * (1 - \mu) * I_{v2} - \rho * P_v \quad [11]$$

$$\frac{dP_s}{dt} = \varphi_1 * (I_{s1} + Q_s) + \varphi_2 * (1 - \mu) * I_{s2} - \rho * P_s \quad [12]$$

$$\frac{dR}{dt} = \rho * (P_v + P_s) \quad [13]$$

$$\frac{dD}{dt} = \varphi_2 * \mu * (I_{v2} + I_{s2}) \quad [14]$$

$$\frac{dW}{dt} = \omega * (Q_v + I_{v1} + I_{v2} + Q_s + I_{s1} + I_{s2} + P_v + P_s) - \delta * W \quad [15]$$

Some model parameters are described by the following equations:

$$\lambda = \frac{R}{N * (\frac{1}{\varphi_1} * m + \frac{1}{\varphi_2} * (1 - m))} \quad [16]$$

$$\gamma_{v1} = E_v * [1 - (1 - m) * (1 - VE_m)] \quad [17]$$

$$\gamma_{v2} = E_v * (1 - m) * (1 - VE_m) \quad [18]$$

Table 1: Parameter values used in each model simulation. These values were obtained from the literature or calibrated during model construction where indicated with *. A dash (-) indicates the intervention pertaining to that parameter was not in place during the that time period.

Parameter	Definition	No Vaccination 1	No Vaccination 2	Vaccine Rollout	Delta	Omicron	Source
γ_s	Rate of transition from exposed to infectious state	1/7 days	1/7 days	1/7 days	1/7 days	1/7 days	(Li et al., 2020)
φ_1	Rate of transition from infectious to post-infectious state (mild-moderate disease)*	1/8 days	1/8 days	1/8 days	1/4 days*	1/8 days	(Hu et al., 2021), *Calibrated
φ_2	Rate of transition from infectious to post-infectious state (severe disease)*	1/14 days	1/14 days	1/14 days	1/8 days*	1/14 days	(Hu et al., 2021), *Calibrated
ρ	Recovery rate	1/14 days	1/14 days	1/14 days	1/14 days	1/14 days	(Hu et al., 2021; Wu et al., 2020; Zhang et al., 2021)
ω	Shedding rate	876 $\log_{10}$ gc/capita/day	876 $\log_{10}$ gc/capita/day	876 $\log_{10}$ gc/capita/day	876 $\log_{10}$ gc/capita/day	876 $\log_{10}$ gc/capita/day	(Curtis et al., 2020; Schmitz et al., 2021)
δ	Rate of SARS-CoV-2 die-off in wastewater	1/1.5 days	1/1.5 days	1/1.5 days	1/1.5 days	1/1.5 days	(Bivins et al., 2020)
VE_i	Vaccine effectiveness against infection	-	-	90%	90%	50%	(Collie et al., 2022)
VE_m	Vaccine effectiveness against severe infection	-	-	6%	6%	40%	(Collie et al., 2022)
R	Reproduction number*	1.9*	6.5*	3.5*	8.5*	2*	*Calibrated
m	Proportion of infections with mild-moderate disease	0.932	0.932	0.932	0.922	0.973	(Iuliano et al., 2022)
q_v	Proportion of mild-moderate cases caught by screening and put in isolation	-	0.657	0.657	-	-	(Yifei Wang et al., 2022)
q_s	Proportion of mild-moderate cases caught by screening and put in isolation	-	0.657	0.657	0.657	0.657	(Yifei Wang et al., 2022)

ξ	Rate of vaccination	-	-	0.005 /day	-	-	(*us_state_vaccinations*, 2022)
μ	Proportion of deaths from severe disease	0.054	0.054	0.054	0.076	0.021	(Iuliano et al., 2022)
Volume	Volume of wastewater sampling area used to calculate concentration	50,000 mL	50,000 mL	50,000 mL	125,000 mL	125,000 mL	Estimated

These equations are used to initialize the exposed compartments when vaccination is involved in model dynamics:

$$n = number\ of\ cases\ reported\ within\ the\ first\ 7\ days\ of\ model\ time\ period$$

$$E_v = n * 0.97 * (1 - VE_i) \quad [19]$$

$$E_s = n - E_v \quad [20]$$

Table 2: Initial conditions used for each model simulation. Susceptible and vaccinated compartments were initialized based on counts from Emory University of the number of students on campus each semester and the proportion of students that were fully vaccinated. Other population compartments were initialized from Emory University case reporting numbers, and the wastewater compartment was calculated from case reporting numbers, virus shedding rate, and virus die-off rate.

Compartment	No vaccination 1	No vaccination 2	Vaccine rollout	Delta	Omicron
S	4545	4318	4159	384	347
V	NA	NA	0	12,453	12,286
E_v	NA	NA	0	14	66
E_s	4	42	51	125	70
Q_v	NA	NA	0	17	178
I_{v1}	NA	NA	0	0	0
I_{v2}	NA	NA	0	0	0
Q_s	8	41	22	2	20
I_{s1}	0	0	0	0	0
I_{s2}	0	0	0	0	0
P_v	NA	NA	0	0	185
P_s	13	48	227	18	6
R	55	282	441	163	367
D	0	0	0	0	0
W	27,594	174,762	287,365	47,304	511,146

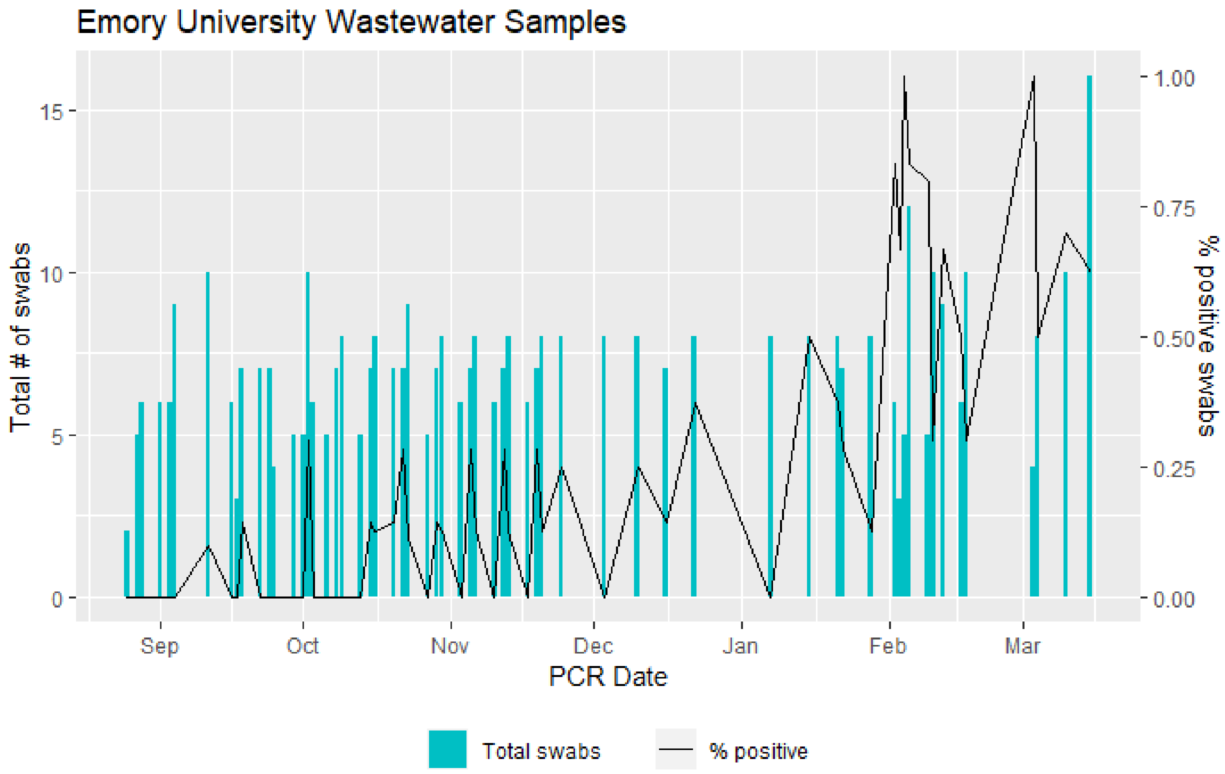

Figure 3: Sampling for presence of SARS-CoV-2 RNA in Emory University wastewater. An average of seven swabs were collected from manholes around Emory University campus each sampling day from August 2020 to March 2021, with a minimum of two swabs collected on 24 August 2020 and a maximum of 16 swabs collected on 15 March 2021. The proportion of swabs that tested positive for presence of SARS-CoV-2 RNA generally increased over time, starting with zero positive swabs in the first six days of sampling and reaching 100% positive swabs on 04 February 2021 and 03 March 2021. Over the entire period, an average of 23% of swabs were positive on each sampling day.

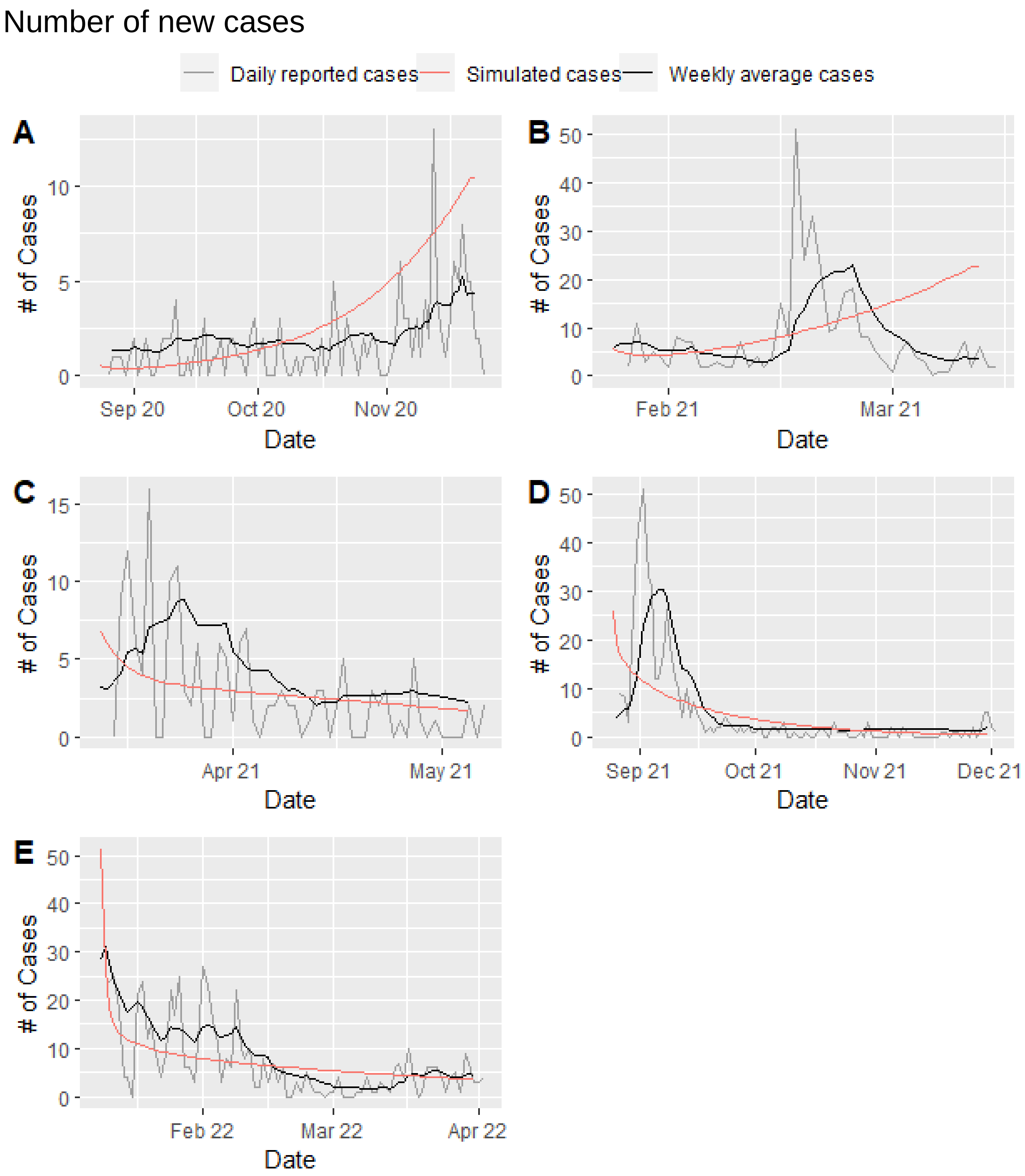

Figure 4: New cases reported by Emory University and simulated cases for the model periods of no vaccination 1 (A), no vaccination 2 (B), vaccine rollout (C), Delta (D), and Omicron (E). Daily reported cases are the number of cases reported by Emory University each day. Weekly average cases are the weekly rolling average of reported cases calculated by Emory University. Simulated cases are the number of individuals that migrated from the exposed to infectious stages of the model each day.

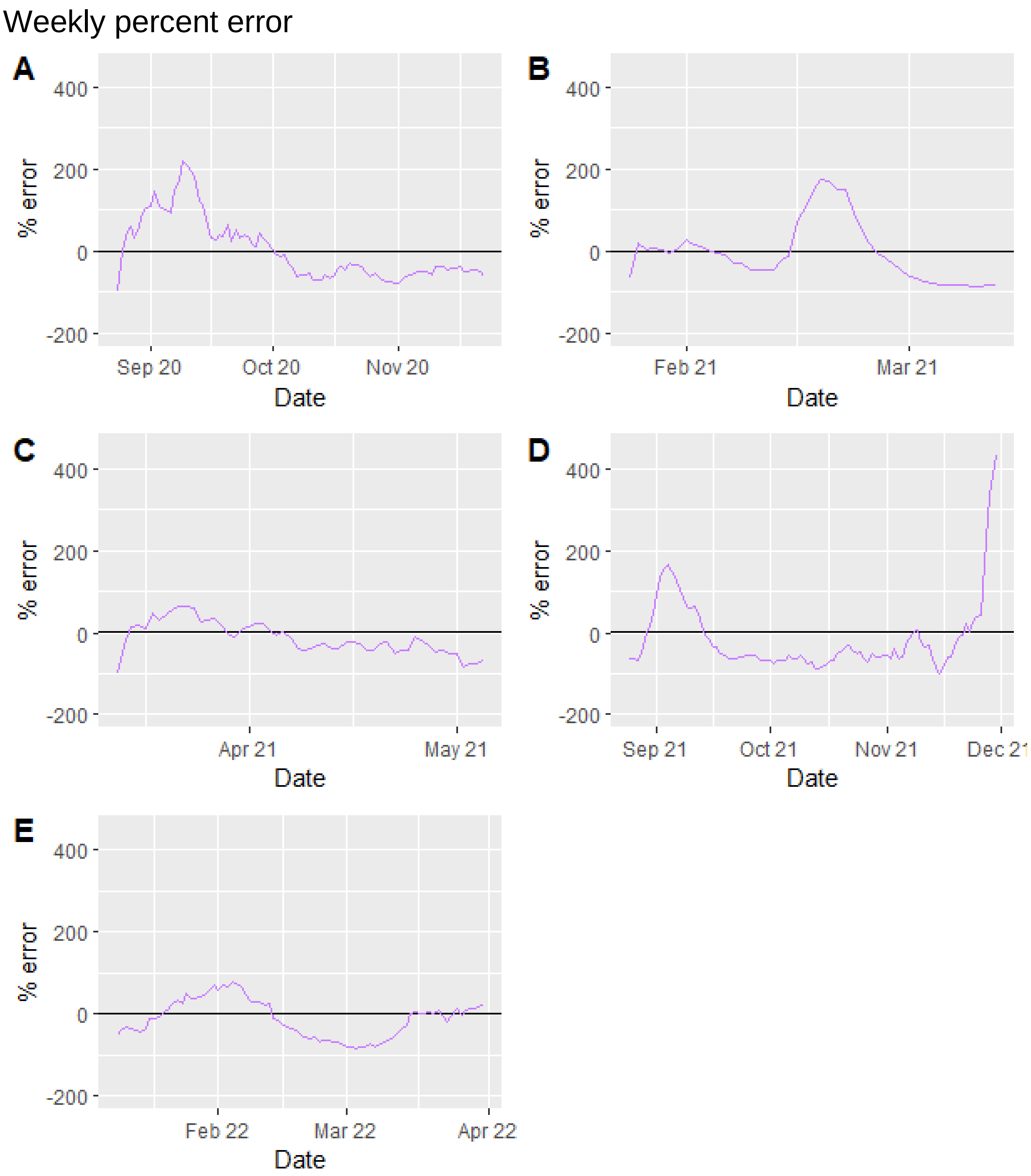

Figure 5: Weekly percent error between rolling weekly average of cases observed by the simulation and rolling weekly average of cases expected by Emory University case reporting adjusting for a two-day reporting lag for the model periods of no vaccination 1 (A), no vaccination 2 (B), vaccine rollout (C), Delta (D), and Omicron (E). The spike in percent error in no vaccination 2 in early February follows President's Day weekend, which may have increased travel and transmission in Atlanta, even though Emory University students did not have a long weekend. The other large spike, in the last week of the Delta period, is likely due to an increase of cases when students returned to campus after traveling during the Thanksgiving break.

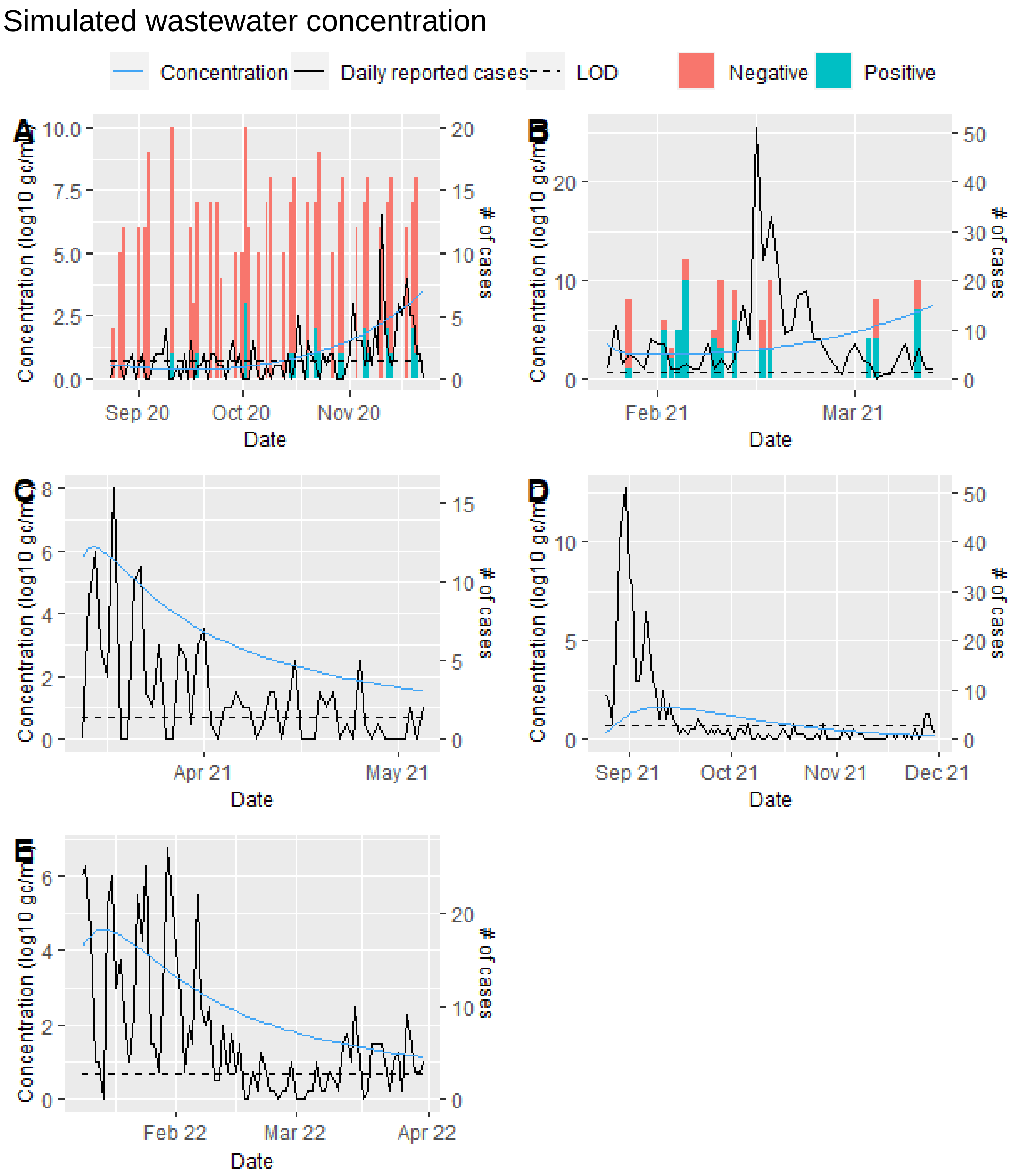

Figure 6: The wastewater concentration (log$_{10}$ gc/mL) for the model periods of no vaccination 1 (A), no vaccination 2 (B), vaccine rollout (C), Delta (D), and Omicron (E). Concentration was estimated using the simulated amount of SARS-CoV-2 present in the wastewater environment each day and the estimated volume of a sampling area. The number of positive and negative swabs collected each sampling day is aligned on the left axis. Wastewater sampling occurred

only in the first two periods. The limit of detection (LOD) for Moore swabs was 0.7 $\log_{10}$ gc/mL. Daily reported cases are reported from Emory University.

Table 3: Results of the model simulations for each time period. Vaccines were not available to Emory University students during the no vaccination 1 and 2 periods.

	No vaccination 1	No vaccination 2	Vaccine rollout	Delta	Omicron
Duration (days)	91	47	54	98	81
Total infected	277	500	157	411	610
Vaccinated	-	-	1	226	516
Unvaccinated	-	-	156	185	94
Mild-Moderate	258	466	146	380	599
Vaccinated	-	-	1	210	508
Unvaccinated	-	-	145	170	91
Severe	19	34	11	31	11
Vaccinated	-	-	0	17	8
Unvaccinated	-	-	11	14	3
Avg Concentration ($\log_{10}$ gc/mL)	1.1	3.8	3.2	0.8	2.5
% days over LOD	45%	100%	100%	55%	100%

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