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Making waves: Integrating wastewater surveillance with dynamic modeling to track and predict viral outbreaks

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ABSTRACT

Wastewater surveillance has proved to be a valuable tool to track the COVID-19 pandemic. However, most studies using wastewater surveillance data revolve around establishing correlations and lead time relative to reported case data. In this perspective, we advocate for the integration of wastewater surveillance data with dynamic within-host and between-host models to better understand, monitor, and predict viral disease outbreaks. Dynamic models overcome emblematic difficulties of using wastewater surveillance data such as establishing the temporal viral shedding profile. Complementarily, wastewater surveillance data bypasses the issues of time lag and underreporting in clinical case report data, thus enhancing the utility and applicability of dynamic models. The integration of wastewater surveillance data with dynamic models can enhance real-time tracking and prevalence estimation, forecast viral transmission and intervention effectiveness, and most importantly, provide a mechanistic understanding of infectious disease dynamics and the driving factors. Dynamic modeling of wastewater surveillance data will advance the development of a predictive and responsive monitoring system to improve pandemic preparedness and population health.

1. Introduction

Emerging and re-emerging diseases, such as COVID-19, have and continue to devastate the world (Dong and Soong, 2021; Morens et al., 2004). With increasing human mobility, highly contagious diseases can quickly develop into destructive pandemics causing great loss of human lives and damage to the world economy (Gao, 2020; Kraemer et al., 2020; Li et al., 2021). Effective surveillance methods are imperative to track and aid in preventing and controlling such outbreaks. Following several cholera pandemics throughout Asia, Europe, and America in the 19th century, the world realized the importance of wastewater treatment, leading to the rapid development of the modern sewage and wastewater surveillance systems that we know today (Life in the Lab, 2021; Levy et al., 2023). The beginning of the 21st century marked the first time when scientists began to utilize the sewage infrastructure to track drug usage and the prevalence of poliovirus and enteroviruses (Brouwer et al., 2018; Daughton, 2018; Duintjer Tebbens et al., 2017; Manor et al., 2014). Yet, the development of the field is in its infancy.

In 2019, the first case of COVID-19 was reported in Wuhan China, which then rapidly spread globally (Li et al., 2021; Sanche et al., 2020; Zhu et al., 2020). While SARS-CoV-2 can cause severe complications in the respiratory system and even death, a substantial fraction of infected individuals are asymptomatic or subclinical (Mizumoto et al., 2020; Oran and Topol, 2021). Furthermore, unlike other respiratory infections such as influenza, infected individuals can take up to 14 days before showing symptoms (Symptoms of COVID-19 |CDC, 2022). These characteristics of SARS-CoV-2 infection coupled with an initial lack of an efficient tool and resources for SARS-CoV-2 testing means that case

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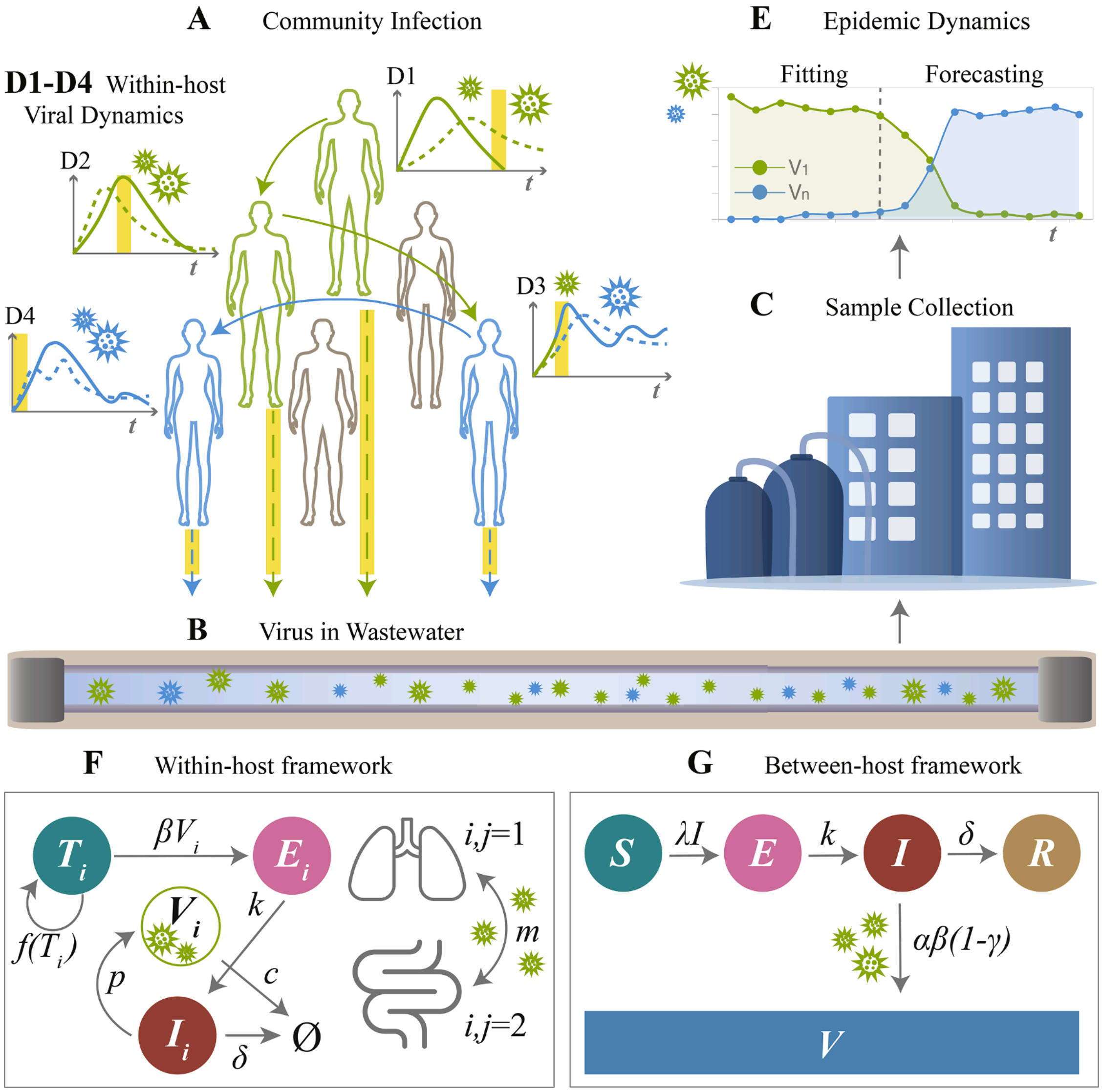

Fig. 1. An integrated framework to incorporate wastewater data into epidemic models. (**A**) Illustration of community transmission denoted by solid arrows. Green is the dominant viral strain and blue is the emerging viral strain. (**B-C**) Viruses shed into wastewater and travel to a wastewater treatment plant, denoted by dashed arrows. (**D**) Within-host viral dynamics affect the community transmission and the level of virus in wastewater. D1-D4: heterogeneity of viral load. The four plots illustrate the temporal dynamics of viral load in the respiratory tract (solid curve) and gastrointestinal tract (dashed curve), given the differences between individuals, locus of infection (respiratory vs. gastrointestinal tract), and viral strains. The viral shedding to wastewater (highlighted) is temporally related to the highlighted portion in the viral load profiles (D1-D4). (**E**) Dynamic model with wastewater data can be used to understand and predict the progression of the pandemic, such as the emergence of new variants. (**F-G**) Modeling framework representations of Eqns. 1-2 (**F**) and Eqns. 3-4 (**G**).

report data was considerably lagging the progression of the pandemic. A new tool for monitoring the spread of the pandemic to address these issues was needed.

Reports of SARS-CoV-2 detection in the stool of infected individuals and wastewater samples began to surface in early 2020, which led to increasing interest in the use of wastewater surveillance to track the SARS-CoV-2 pandemic (Ahmed et al., 2020; Chen et al., 2020; Jones et al., 2020; Mantilla-Calderon et al., 2022; Medema et al., 2020; Randazzo et al., 2020; Wölfel et al., 2020a; Wu et al., 2020). Unlike case report data, wastewater surveillance seemingly bypasses the challenge of underreporting and lag in case report information, which offers an opportunity for epidemiologists and public health officials to track and intervene in the spread of the pandemic in near real-time (Bivins et al., 2020; Diamond et al., 2022; Gitter et al., 2023; Mantilla-Calderon et al., 2022; Peccia et al., 2020; Thompson et al., 2020; Wu et al., 2022a, 2022b).

Mechanistic dynamic models are a fundamental tool to understand and forecast the epidemiology of infectious diseases. The strength of dynamic models lies in the ability to quantify the general trajectory of the pandemic under different real-world scenarios, or counterfactual analyses. When dynamic models are applied correctly, they can help epidemiologists to better develop appropriate interventions to control the spread of the pandemic (Eikenberry et al., 2020; Ke et al., 2021a; Kucharski et al., 2020; Saad-Roy et al., 2021; Sanche et al., 2020; Wagner et al., 2022; Zelner and Eisenberg, 2022). However, while dynamic models are a standard tool in epidemiology, they were not developed extensively for the integration of wastewater surveillance data prior to the COVID-19 pandemic. Dynamic models can help to overcome some fundamental obstacles in connecting wastewater surveillance data and case report data. Hence the goal of this paper is to illuminate the complementary nature of wastewater surveillance data and dynamic models (Fig. 1) to raise interest and further the development of wastewater-based epidemiology.

2. Challenges of using wastewater surveillance data for quantitative epidemiological inference

One of the main applications of wastewater surveillance is to understand an outbreak's burden and progression at the population level. A common approach to estimate the number of infected cases in the sewershed is by back-calculation using viral concentrations in wastewater multiplied by flow rate during the sampling day and divided by virus shed per person per day (Ando et al., 2023; Cavany et al., 2022; Guo et al., 2022; Kaplan et al., 2022; Petala et al., 2022; Schmitz et al., 2021; Wu et al., 2022b; Xiao et al., 2022). This approach is heavily dependent on the accuracy of the measured viral shedding rate. Viral RNA or DNA in wastewater is excreted from infected individuals in exposed, infectious, and recovered phases. Viral shedding is dynamic and varies across infected individuals; however, obtaining the shedding data throughout the infection course is often challenging, especially during the pre-symptomatic phase. Such a viral shedding profile is fundamental for accurate inference of prevalence from wastewater data, estimating the number of cases in each phase, and forecasting viral transmission with or without interventions.

Wastewater surveillance data comes with its own set of challenges such as variation in viral shedding rate and duration between individuals, different variants, vaccination coverage, vaccine efficacy, viral travel time and degradation rate in the sewer, fluctuation in wastewater flow rate, viral recovery efficiency and detection limits of experimental protocols (Amoah et al., 2022; Gitter et al., 2023; Phan et al., 2023b; Polcz et al., 2023; Wu et al., 2022a). To what degree those parameters contribute to wastewater data-based epidemiological inference (prevalence, transmission dynamics, and prediction) is mostly unexplored. To fully address these issues requires careful examination of each parameter.

These limitations greatly constrain the practical value of wastewater surveillance data for public health practice. We here propose the use of two types of dynamic models, within-host (viral dynamic) and between-host (epidemic) models, to address these limitations.

3. Within-host viral dynamics is the key to quantifying the viral shedding profile

The theory of within-host viral dynamics emerged from population models of host-parasite interactions near the end of the 20th century in response to the human immunodeficiency virus (HIV) pandemic (Nowak and Bangham, 1996; Perelson et al., 1996) and developed extensively to better understand HIV, hepatitis B virus (HBV) and other transmissible viral diseases (Ciupe, 2018; Conway et al., 2019; Ho et al., 1995; Perelson et al., 1997; Ramratnam et al., 1999; Stafford et al., 2000). Advances in this field have allowed for improvement in treatment protocols, such as the current antiretroviral therapies for people living with HIV (Ho et al., 1995). During the COVID-19 pandemic, within-host viral dynamics of SARS-CoV-2 have provided valuable insights into the course of infection, including viral shedding in the respiratory tract (Ke et al., 2021b), duration of infectiousness (Heitzman-Breen and Ciupe, 2022; Ke et al., 2022a; Marc et al., 2021), the emergence of viral resistance and rebound (Choudhary et al., 2022), heterogeneity in outcomes and severity (Chatterjee et al., 2022; Sanche et al., 2022), antibody responses and vaccine efficacy (Padmanabhan et al., 2022), and factors that affect treatment effectiveness (Czuppon et al., 2021; Gonçalves et al., 2020; Goyal et al., 2020; Kim et al., 2021; Lingas et al., 2022; Perelson et al., 2023; Prague et al., 2022). The study of within-host viral dynamics in COVID-19 has primarily centered on the respiratory tract, yet the evidence for the application of these models to shed light on the viral shedding profile of the gastrointestinal tract is compelling.

SARS-CoV-2 infects mainly epithelial cells that express angiotensin-converting enzyme 2 (ACE-2) receptors in the respiratory tract often with the help of the transmembrane serine protease type 2 (TMPRSS2) (Jackson et al., 2022). Intestinal infections of SARS-CoV-2 have also been evidenced in human intestinal cell lines (Zupin et al., 2022) and organoids (Lamers et al., 2020), *in vivo* animal models (Kim et al., 2020; Shi et al., 2020; Young il et al., 2020), and in the gastrointestinal tract of asymptomatic patients by endoscopy (Cherne et al., 2022; Guo et al., 2021; Xiao et al., 2020). Furthermore, infection in the gastrointestinal tract also prompts a similar immune response to that of the respiratory tract (Stanifer et al., 2020). Thus, standard viral dynamic models that incorporate target cells, infected cells, viruses, and immune responses, are adaptable to describe viral infection in the gastrointestinal tract (Perelson and Ke, 2021).

The community transmission is driven by the individual within-host viral infection dynamics (Fig. 1A, D1-D4), which has significant variability among individuals (Ke et al., 2022b; Killingley et al., 2022a; Puhach et al., 2022). However, it is generally feasible to quantify a population-averaged viral shedding profile for the purpose of epidemiological modeling and inferences (Feng et al., 2012; Lin et al., 2022; Phan et al., 2023b). This is commonly achieved using phenomenological functions such as the beta and gamma distributions, or other specialized functions (Huisman et al., 2022; Phan et al., 2023b; Wu et al., 2022b; Xiao et al., 2022). However, if one intends to build a dynamic model of the within-host viral infection process, then a possible initial description of the coupling of viral infections between the respiratory and gastrointestinal tracts may take the form (Fig. 1F):

$$T_i' = f_i(T_i) - \beta_i V_i T_i;\; E_i' = \beta_i V_i T_i - k_i E_i;\; I_i' = k_i E_i - \delta_i I_i; \tag{1}$$

$$V_i' = p_i I_i - c_i V_i - m_{ij} V_i + m_{ji} V_j,\ \text{where } i, j = 1, 2 \tag{2}$$

and superscript $'$ denotes a derivative with respect to time. This set of equations is inspired by models of SARS-CoV-2 infection in the upper and lower respiratory tracts (Ke et al., 2020). Here, the subscripts i and j indicate the respiratory tract when they equal 1 ($i, j = 1$) and gastrointestinal tract when they equal 2 ($i, j = 2$). T_i denotes the target cell population (cells), which has natural dynamics given by the function $f_i(T_i)$ (cells per day) that incorporates cell death, generation by differentiation of precursors, proliferation, etc. Viruses V_i (RNA copies per mL) infect target cells at per capita rate β_i (mL per RNA copies per day). The infected cells are initially in the eclipse phase E_i (cells), when they are infected but have not yet produced viruses. After an average eclipse duration of $1/k_i$ (days), infected cells in the eclipse phase transition into productively infected cells I_i (cells), which produce viruses at rate p_i (RNA copies per mL per day per cell) and die at per capita rate δ_i (per day) due to a combination of natural death and viral cytopathic effects. Note that the viral migration terms m_{ij} and m_{ji} (per day) represent (viral) movement from the i-tract to the j-tract, or vice versa, respectively. Free virus V_i is also cleared at rate c_i (per day). A schematic for Eqn. (1) - (2) is presented in Fig. 1F. Assuming the viral dynamic parameters are the same in the two tracts ($\beta_1 = \beta_2,\ p_1 = p_2,\ c_1 = c_2$), then possible explanations for the prolonged presence of SARS-CoV-2 in the gastrointestinal tract based on this model are slower death rate of infected cells ($\delta_2 < \delta_1$), or faster regeneration rates of target cells, i.e., $f_2(T_2) > f_1(T_1)$. However, while these explanations are perhaps feasible, this simple description of the viral infection process can be improved by incorporating immune responses, explicit spatial structure via partial differential equation or patch-models (Gallagher et al., 2018; Gillman et al., 2021), and other distinct features of the gastrointestinal tract.

The intestinal spatial architecture could also play a crucial role in the trajectory of viral growth and explain the slower viral clearance in the gastrointestinal tract. The geometry and size of the respiratory and gastrointestinal tracts differ substantially, with the elongated gastrointestinal tract potentially leading to a more sequential progression of local infection events. Thus, the viral infection process may take place slower in the gastrointestinal tract compared to respiratory tract. Dynamic models should take into consideration the importance of spatial structure and transport mechanisms like peristalsis, as they may impact the persistence of SARS-CoV-2 in stool samples (Gallagher et al., 2018). The unique immune kinetics in the gastrointestinal tract, shaped by the coexistence of gut microbiota should also be considered (Belkaid and Hand, 2014; Wang et al., 2022; Yeoh et al., 2021). This can be achieved by including factors such as antigen presentation, inflammatory responses, cell proliferation, epithelial cell heterogeneity, cell-to-cell transmission, etc. (Graw and Perelson, 2016; Okumura and Takeda, 2016; Round and Mazmanian, 2009).

Enhancing our understanding of the within-host infection process can help facilitate a stronger connection of wastewater surveillance data with case report data, as is the case for standard nasal swab testing (Ke et al., 2021b). For example, within-host viral dynamic models can shed light on why virus is only detected in the fecal specimens from about half of the infected individuals (Cheung et al., 2020; Natarajan et al., 2022), the mechanisms behind the prolonged persistence of SARS-CoV-2 in stool samples, and the relative viral shedding during the infectious and recovered phases in infected individuals with varying severity or symptoms. Answering these questions may explain the temporal variations in lead-time and determine the underreport rate to provide accurate estimates of new infections and quantify the probability of resurgence (Cavany et al., 2022; D'Aoust et al., 2021; Lee et al., 2022; Phan et al., 2023a). Finally, the lead time and correlation of wastewater surveillance data relative to case report data are often quantified using statistical comparisons, which lacks a standard definition (Bibby et al., 2021; Krivoňáková et al., 2021; Olesen et al., 2021; Peccia et al., 2020; Vallejo et al., 2022; Wu et al., 2022b; Xiao et al., 2022). Using within-host models, a baseline lead time can be rigorously defined by examining the asynchronization between the infection progression and the viral shedding curves (V_1 and V_2 in Eqn. 1-2, respectively), similar to the suggestion by Bibby et al. (Bibby et al., 2021). Other factors such as reporting delay can be included to improve the inference from wastewater surveillance data for specific regions and applications.

4. Integration of between-host dynamic models to maximize the value of wastewater surveillance data

One of the first applications of dynamic models in epidemiology took place nearly 100 years ago in Kermack and McKendrick's seminal work on the SIR (Susceptible – Infected – Recovered) model (Bacaër, 2011; Kermack and McKendrick, 1927). Since then, these between-host dynamic models have become a powerful tool for epidemiologists and public health officials to prevent and control outbreaks (Lessler and Cummings, 2016). In practice, dynamic models are trained on case report data and then used to forecast likely trajectories of an outbreak and estimate key epidemiological quantities such as the basic reproduction number R_0. Accurate estimates of true disease prevalence are often feasible when disease-related symptoms are distinct and easy to detect, such as Ebola (Pell et al., 2018). Unfortunately, the high fraction of asymptomatic individuals and the delay in symptom onset for SARS-CoV-2 imply that dynamic models trained on case report data – without accounting for the unknown number of asymptomatic cases - may considerably lag behind and underestimate the true prevalence of the pandemic.

Wastewater surveillance data can overcome the issues of underreporting and time lag in clinical surveillance. Thus, it can provide a near real-time description of an ongoing outbreak. Incorporating wastewater surveillance data in dynamic models, therefore, should be ideal for diseases such as SARS-CoV-2. However, few studies have attempted to combine wastewater surveillance data with dynamic models (Ahmadini et al., 2022; Brouwer et al., 2022a; Jin Joung et al., 2022; Klaassen et al., 2023; Mattei et al., 2023; McMahan et al., 2021; Nourbakhsh et al., 2022; Pájaro et al., 2022; Pell et al., 2023; Phan et al., 2023b; Polcz et al., 2023; Proverbio et al., 2022). Phan et al. (Phan et al., 2023b) proposed a dynamic modeling framework based on segmentation of the viral shedding profile to connect viral RNA measurement in wastewater with case report data. We briefly describe the model here starting with a basic SEIR (Susceptible-Exposed-Infectious-Recovered) model (Fig. 1G):

$$S' = -\lambda SI;\ E' = \lambda SI - kE;\ I' = kE - \delta I;\ R' = \delta I - \sigma R. \tag{3}$$

In this model, S denotes the susceptible population, with $S(0)$ representing the initial sewershed human population size; E is the infected but not yet infectious population (or the exposed population); and I is the infectious population. The R compartment includes the recovered individuals. Note that these classifications are based on the respiratory tract infection, in particular the V_1 compartment in Eqn. (1) – (2). Susceptible people are infected by the infectious class at a rate λI. Exposed individuals become infectious at a rate k. Infectious individuals recover at a rate δ. Recovered individuals clear gastrointestinal tract infection at a rate σ. The units for the four rates can be per day (day^{-1}). Lastly, since viral shedding correlates with viral load, and infectious individuals should have the highest viral load (Killingley et al., 2022b; Wölfel et al., 2020b), we may assume that the infectious individuals contribute the most to the viral shedding in wastewater. Note that this assumption is only for the purpose of demonstration, ideally this connection should be established based on within-host viral dynamic studies. With this assumption, the viral load in wastewater can be thought of as proportional to the number of all individuals who are currently infectious (I).

$$V' = \alpha\beta(1-\gamma)I. \tag{4}$$

V is the measurable cumulative viral RNA (RNA copies) in wastewater, which is equal to the measured viral concentration (RNA copies per mL of wastewater) multiplied by the daily influent flow rate (mL of wastewater). Infectious individuals shed virus at a rate $\alpha \times \beta$, where α is the daily fecal load (gram) and β is the average viral shedding rate per infectious individual per daily fecal load (log10 viral RNA copies per gram stool per day). γ is the fraction of viral loss while traveling in the sewer pipes, so only a fraction $(1-\gamma)$ of virus can be detected in the wastewater sample at the time of measurement. Since V is the cumulative viral RNA, its difference over every measurement interval can be fitted to the viral RNA measurements in wastewater to estimate the transmission parameters (section 2.7 in the study by Phan et al., 2023). We then can introduce a proxy variable to keep track of the cumulative number of infections (prevalence), for example $C' = \lambda IS$. The daily difference in C is the model predicted daily incidence. Phan and colleagues have shown that it is sufficient to fit the model to only wastewater data to recapitulate the trend in case report data and revealed the underreporting rate by comparing model predicted daily incidence with case report data (Phan et al., 2023b). This approach requires a good knowledge of the viral shedding profile, the within-host infection progression, and other factors such as the chemical and temperature dependent viral loss rate. On the other hand, fitting to only wastewater data avoids the high uncertainty in case report data during the early and late phases of an outbreak that can cause issues with model inference.

For simplicity, γ can be treated as a constant in Eqn. (4); however, it can also be formulated to consider additional factors, such as wastewater temperature, travel time, chemical composition of wastewater, and sewershed information (Petala et al., 2021; Phan et al., 2023b). Equation (4) is a simple demonstration of the framework, which can be augmented to include the viral shedding from the recovered or exposed individuals in the model formulation (Arts et al., 2023; Brouwer et al., 2022b; Phan et al., 2023a). More general formulations of the SEIR-V model using convolution with age-of-infection (Demongeot et al., 2023) and viral shedding functions are possible (Mattei et al., 2023; Wu et al., 2022b), but require an accurate description of the viral dynamics in both the respiratory and gastrointestinal tracts. Finally, while various factors influencing SARS-CoV-2 RNA concentration from shedding to sampling stages (Bertels et al., 2022) can be modeled explicitly (Petala et al., 2021), careful consideration of these factors to build models with complexity commensurate with the available data is crucial to avoid model identifiability issue (Chowell, 2017; Ciupe and Tuncer, 2022) and

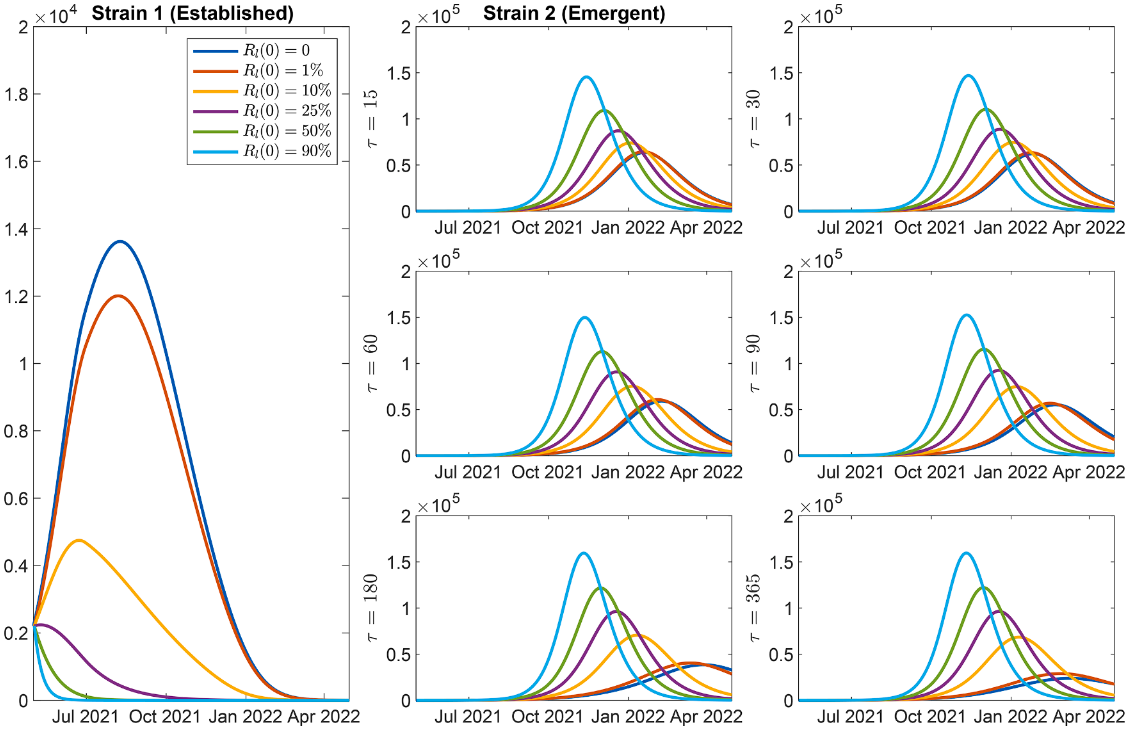

Fig. 2. The emergence of a new variant inferred from dynamic modeling of wastewater surveillance data. Simulations based on the multi-variant strain model fitted to SARS-CoV-2 concentrations in wastewater (Pell et al., 2023). The curves show daily incidence. R_l is the fraction of individuals that are immune to the initially dominant strain (strain 1). τ (days) is the average duration of immunity (against infection by the emerging strain 2) due to either infection by strain 1 or vaccination.

to achieve precision wastewater-based epidemiology.

Besides infection prevalence, the wastewater-based epidemic model can also be used to estimate key epidemic indicators such as the basic and effective reproduction numbers (Huisman et al., 2022). Since the concept of reproduction number was originally developed for dynamic models (Bacaër, 2011), it is straightforward to estimate these quantities using dynamic models. The basic reproduction number for the SEIR-V model (3) – (4) is given by $R_0 = \frac{\lambda}{\delta}S(0)$, whereas the effective reproduction number is $R_e(t) = \frac{\lambda}{\delta}S(t)$. Many factors may alter estimations of reproduction number over the course of an outbreak (Delamater et al., 2019). Nonetheless, simple models can provide a rough estimate of the reproduction number to gauge the transmissibility of a new outbreak.

Since early detection of new variants is possible using wastewater surveillance data (Bar-Or et al., 2021; Carcereny et al., 2022; Crits-Christoph et al., 2021; Herold et al., 2021; Jahn et al., 2022; Karthikeyan et al., 2022; Lee et al., 2021; McGowan et al., 2022; Vo et al., 2022), dynamic models can provide early estimate the fitness of emerging variants (Boyle et al., 2022; Pell et al., 2023). Using the model introduced by Pell et al. (Pell et al., 2023), one can look at the emergence of a new variant under various hypothetical scenarios, such as different immune-waning rates (Fig. 2). If sufficient data such as the relative transmission rate and the timing of appearance of an emerging variant can be obtained early from wastewater data, then one may be able to predict the likelihood of a new surge.

The potential of using wastewater surveillance data with dynamic models extends beyond correlation studies. Arguably the most useful aspect of dynamic models is their ability to predict a set of likely outcomes based on various real-world scenarios and assumptions. For instance, once a dynamic model is fitted to the available data, one can study different interventions with the model and forecast the expected effectiveness of these interventions. The inherent advantages of wastewater surveillance data suggest that its implementation in dynamic models would allow researchers to bypass typical difficulties associated with case report data and to test different control measures in near real-time.

5. Conclusion

The COVID-19 pandemic acutely identified gaps and limitations in our current means for addressing public health crises. We believe the integration of within-host and between-host epidemic models is fundamental to achieve a mechanistic understanding of wastewater-based surveillance data for quantitative epidemiological inference. Combining wastewater surveillance data and dynamic models will further advance the development of a predictive and responsive monitoring system to enhance pandemic preparedness and population health. The key conclusions are:

- Dynamic models are a powerful tool to implement and maximize the potential of wastewater surveillance data to inform public health preparedness.
- Within-host viral dynamics is the key to establishing the viral shedding profile, thus facilitating a better integration of wastewater surveillance data into epidemic models and improving predictability.
- Wastewater surveillance data provides unique information, bypassing the difficulties of time lag and underreporting of case data, thus enhancing the utility and applicability of dynamic models.

Declaration of Competing Interest

The authors declare they have no competing interests.

Data availability

No data was used for the research described in the article.

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