9-10-2021

Simulating Influenza Epidemics with Waning Vaccine Immunity

Chun-Miin Chen
Bucknell University

Alia C. Stanciu
Bucknell University, acs023@bucknell.edu

Quality Improvement Study

Medicine®

OPEN

Simulating influenza epidemics with waning vaccine immunity

Chun-Miin (Jimmy) Chen, PhD*, Alia C. Stanciu, PhD

Abstract

Observational studies indicate that vaccine-induced immunity can decline over time. However, few researchers have incorporated this kind of waning effect into their virus spread models. In this study, we simulate an influenza epidemic that considers the effects of waning immunity by fitting epidemiological models to CDC secondary historical data aggregated on a weekly basis, and derive the transmission rates at which susceptible individuals become infected over the course of the influenza season. Using a system of differential equations, we define four groups of individuals in a population: susceptible, vaccinated, infected, and recovered. We show that a larger number of initially infected individuals might not only bring the influenza season to an end sooner but also reduce the epidemic size. Moreover, any influenza virus that entails a faster recovery rate does not necessarily lead to a smaller epidemic size. We illustrate how simulation helps in understanding the effects of influenza epidemiological model in the presence of waning influenza vaccine immunity.

Abbreviations: CDC = Centers for Disease Control and Prevention, SIR = Susceptible-Infectious-Recovered, SVIR = Susceptible, vaccinated, infectious, recovered.

Keywords: influenza, simulation, vaccine, waning immunity

1. Introduction

Influenza is a contagious disease around the world. Year after year, influenza viruses cause illness to people of all ages, which can lead to influenza-related complications or even trigger more severe inflammation in the body. In fact, influenza has been ranked as the eighth leading cause of death in 2017.[1] According to the World Health Organization,[2] annual influenza-related death tolls ranged from 290,000 to 650,000 worldwide. Since 1997, the Centers for Disease Control and Prevention (CDC) have been tracking influenza activity and influenza-related illnesses. In the United States, CDC produces influenza surveillance data, such as the percentage of specimens testing positive for an influenza virus. Every week, all clinical laboratories report to CDC the total number of respiratory specimens tested and the number that tested positive for influenza viruses.

Recently, researchers have started to thoroughly investigate and give special attention to the waning effectiveness of vaccination-induced immunity in the human body. In the 2017 to 2018 influenza season, there were as many as 50 viruses identified for vaccine productions.[3] Given the selected viruses for the new formulation, vaccine manufacturers are racing against time as they produce, test, and distribute the vaccine under a tight schedule.[3–5] Unfortunately, antigenically variable pathogens, such as influenza viruses, are living organisms and are capable of continuously altering the proteins or carbohydrates on their surface and mutating to different strains, thereby potentially escaping from the immunity induced by vaccination.[6] Many studies have reported that vaccine effectiveness within a single influenza season can decrease over time. Kissling et al[7] stated that the decreasing influenza vaccine effectiveness could be the result of virus changes through the season or waning immunity. Pebody et al[8] and Belongia et al[9] advocated the need for developing influenza vaccines that provide better and longer-lasting protection in view of the occurrence of late past-season outbreaks. Hill et al[10] developed a multi-strain transmission model to predict the chronological interactions between the influenza viruses and waning immunity among the population.

In this study, we aim to update classic epidemiological models by explicitly accounting for waning vaccine immunity over time, as well as to examine the effects that various parameters have on the size of the influenza epidemic. Methodologically, we employ simulation, which has been one common approach for understanding the course of an influenza epidemic both in practice and in the literature.[11,12] Goeyvaerts et al[13] developed a seasonal influenza transmission model for evaluating the impact of vaccination on the incidence of infection, disease, and mortality. The authors proposed to directly estimate the values of the seasonal influenza model parameters by fitting the model to

Editor: Antonio Palazón-Bru.

This research was supported in part by a research grant from Bucknell University's Freeman College of Management.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Department of Analytics and Operations Management Bucknell University, Lewisburg, PA.

* *Correspondence: Chun-Miin (Jimmy) Chen, Department of Analytics and Operations Management, Bucknell University, Lewisburg, PA 17837 (e-mail: jimmy.chen@bucknell.edu).*

How to cite this article: Chen CM, Stanciu AC. Simulating influenza epidemics with waning vaccine immunity. Medicine 2021;100:36(e27169).

Received: 12 October 2020 / Received in final form: 4 August 2021 / Accepted: 20 August 2021

http://dx.doi.org/10.1097/MD.0000000000027169

influenza data over multiple influenza seasons. To empirically ground the model, we follow the literature and present a simplified, yet accurate way of fitting influenza seasonal transmission models to publicly available data.[13,14] Using a system of differential equations, we simulate the dynamics of the infection in the population compartmentalized into several groups. The differential equations allow us to define the rates at which susceptible individuals become infectious or infected individuals recover from the disease. Lastly, we conduct an extensive sensitivity analysis to validate our model by varying a wide range of common experimental parameters discussed in the extant literature. This study visualizes the progress of the influenza epidemic not only when vaccine effectiveness wanes, but also when some seemingly favorable change of conditions counter-intuitively contributes to a worsening of the spread of influenza.

The remainder of this article is organized as follows: Section 2 presents the classic susceptible-infectious-recovered (SIR) model that is often used for segmenting a population into groups during an influenza epidemic. In Section 3, we conduct simulation studies using various scenarios for investigating the implications of the empirically based periodic transmission rate, waning vaccination effectiveness, and viciousness of the influenza virus on the size of the epidemic. Finally, in Section 4, we conclude with a summary of our findings.

2. Methods

In this section, we present an approach for fitting a model to influenza data. First, we define the groups that each individual in a population will belong to during an influenza epidemic. Then, using differential equations, we devise a deterministic epidemic model to investigate the implications of varying model parameter values on the severity of the influenza epidemic in the population.

2.1. Model design

Using a sinusoidal function for simulating influenza transmission is not uncommon in epidemiological research.[15–17] For a given empirical data set, we fit the following sinusoidal function to the weekly percentage of the positive laboratory specimens test results over the course of a year:

$$f(t) = A\sin\left[\frac{2\pi}{B(t-C)}\right] + D. \tag{1}$$

where A specifies the amplitude of the oscillation, B defines the time horizon of a complete season, C determines the starting week in a season, D shifts $f(t)$ such that it is positive for all integers $t \in \{1, 2, \ldots, 51, 52\}$, and t indexes the week number in a given year.

We then construct the following optimization problem to get the fitted parameter values for modeling the seasonal influenza phenomenon:

$$\begin{aligned} &\textit{Minimize} && \sum_{t=1}^{52}[x(t) - f(t)]^2 \\ &\textit{subject to} && A, B, C, D \geq 0 \\ & && B \leq 52 \\ & && f(t) \geq 0, \forall t \in \{1, 2, \ldots, 51, 52\}. \end{aligned} \tag{2}$$

We use $x(t)$ to denote the weekly percentage of specimens with positive results in any available historical data set. Once we obtain the optimal parameter values for the decision variables A, B, C, and D, we can use the optimized sinusoidal to derive a contact function that will simulate the rate at which an infected individual transmits the disease to other susceptible individuals. The contact function shows how soon individuals in the population can move between the susceptible, infectious, and recovered groups. In particular, the contact (transmission) rate at which a susceptible individual becomes infected can be obtained by taking the first derivative of Eq. (1) with respect to t. The contact rate, denoted by $\beta(t) = f'(t)$, is a cosinusoidal function of time that informs the various rates of transmission during the influenza season.

2.2. Epidemiological groups

Many studies have used differential equation-based simulation models for simulating the course of influenza.[18–20] Typically, these models place individuals in a predetermined number of groups. In this study, we assume that, at any given time, each individual in the population (N) belongs to one (and only one) of the following groups: susceptible (S), vaccinated (V), infectious (I), or recovered (R).[11,21–24] In particular, S includes those who are healthy but exposed to the risk of contracting influenza from any infectious individuals; V refers to the proportion of individuals in N who are being vaccinated but who can also continuously *leak* to group S; I denotes those who are infectious agents of influenza to those in S; and R denotes those who have contracted influenza, recovered, and are therefore immune for the remainder of the season. Figure 1 exhibits a flowchart that conceptually illustrates to which group the individuals in a population could belong during an influenza epidemic. Note that the dotted line between V and S is the connection that has not yet been considered in most of the influenza-related research so far.

2.3. Differential equations

Given the definition of the SVIR epidemic model, we developed a system of deterministic differential equations that characterizes the rates at which any individual in one group can move to another group[25]:

$$\frac{dS(t)}{dt} = -\beta(t)S(t)\frac{I(t)}{N} + \zeta V(t) \tag{3}$$

$$\frac{dV(t)}{dt} = -\zeta V(t) \tag{4}$$

$$\frac{dI(t)}{dt} = \beta(t)S(t)\frac{(I(t))}{N} - \gamma I(t) \tag{5}$$

$$\frac{dR(t)}{dt} = \gamma I(t). \tag{6}$$

We use ζ to denotes the rate of the decreasing vaccine effectiveness (i.e., waning effect). Studies showed that the vaccine-induced antibody titers can decrease, within a year after the inoculation, to levels encountered in those without protection.[26]

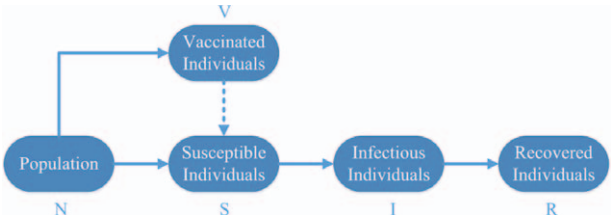

Figure 1. Flowchart of the SVIR model for simulating an influenza epidemic.

Another biological definition of the waning effect is that the antigens on the influenza virion surface (i.e., the target of protective immunity) continually evolves and mutates in the human population. Hence, the influenza strain increasingly differs from its progenitor so that the vaccine-induced immunity against the progenitor can diminish over time.[27] Mathematically, we assume some percent of the vaccinated group can lose the immunity protection and rejoin to the susceptible group. Additionally, γ denotes the inverse of the average length of time an individual stays infectious until moving to the R group. For example, if infected individuals take, on average, four days to recover, then $\gamma = 0.25$. To solve the differential equations, we need the following initial conditions:

$$\begin{aligned} S(t_0) &= (1-\alpha)(N - I_0) \\ V(t_0) &= \alpha(N - I_0) \\ I(t_0) &= I_0 \\ R(t_0) &= 0. \end{aligned}$$

where t_0 denotes the time when the pathogen is introduced in the population, and α represents the level of population immunity given the vaccine's effectiveness and the proportion of susceptible individuals being vaccinated.

Admittedly, some more advanced, complex influenza transmission models with additional parameters will be able to better capture other temporal or systematic variations in the time series data. For example, while the differential equations are popular in simulating the course of influenza transmission, they tend to focus more on modeling the behavior of the groups as a whole. To focus on modeling the probability of individuals being infected given their demographic or community information, agent-based models are capable of considering the stochastic nature of the transmission rate between individuals.[11,24] For more discussions on the differential equations and the agent-based simulation models, see Paleshi et al[12] Our parsimonious mathematical models and differential equations are meant for capturing the main patterns that are evident in the empirical data for the following numerical study.

3. Results

3.1. Empirical data

From the various publicly available data sets on the CDC's website, we focus on the *weekly percentage* of the positive laboratory specimens test results and use those as a proxy for the fraction of the population that is infected. The data were collected from ~300 clinical laboratories located throughout all 50 states, Puerto Rico, Guam, and the District of Columbia. Prior to the 2015 to 2016 influenza season, the weekly influenza update from public health and clinical laboratories were not separately reported. Compared to the clinical laboratories, public health laboratories often receive samples that have already tested positive for an influenza virus at a clinical laboratory.[3] Relatively speaking, the data from clinical laboratories are less distorted than those from public health laboratories in terms of truthfully representing the situations in the population. Therefore, we chose to use data from four influenza seasons, starting with the 2015 to 2016 season, to inform the estimates for our epidemiological model. Figure 2 displays the time-series data of four (over-imposed) influenza seasons consisting of 208 (52×4) weekly fractions of the positive laboratory specimens test results. Overall, the percentages rise rather quickly at the beginning of the season before declining to some low levels starting with week 24. Note that every plot has peaks between week 52 and week 12 and a small uptick before the end of the season, at around week 36.

Because we use only deidentified statistical data aggregated by the CDC at the national level on a weekly basis, no information can be used to uniquely identify each individual. Thus, this study does not involve human subjects in a way that would require review or approval by Bucknell University's Institutional Review Board.

3.2. Model fitting

As opposed to directly imposing some function for the influenza contact (transmission) rate,[20] we *derive* the cosinusoidal contact rate from the empirical data. To this end, we solved the minimization problem in Eq. (2) using MATLAB to obtain A, B, C, and D and specify Eq. (1) (solver *sequential quadratic programming*; www.mathworks.com). In the definition of $x(t)$ in Eq. (2), we use the *average* of the percentages in Figure 2, that is, 52 weekly average ratios across the four influenza seasons. (e.g., $x(1)$ is the average of the four first-week percentages from the data sets.) For the given empirical data set, we fit the sinusoidal function (1), using the model specified in (2) and the parameters $x(t)$ as defined above. The optimized parameter values of A, B, C, and D are 9.4215, 43.0102, 139.2729, and 9.3964, respectively $(R^2 = 0.8992, \text{RMSE} = 2.4671)$. Figure 3 compares the average weekly percent of positivity tests with Eq. (1) given the fitted values of the parameters.

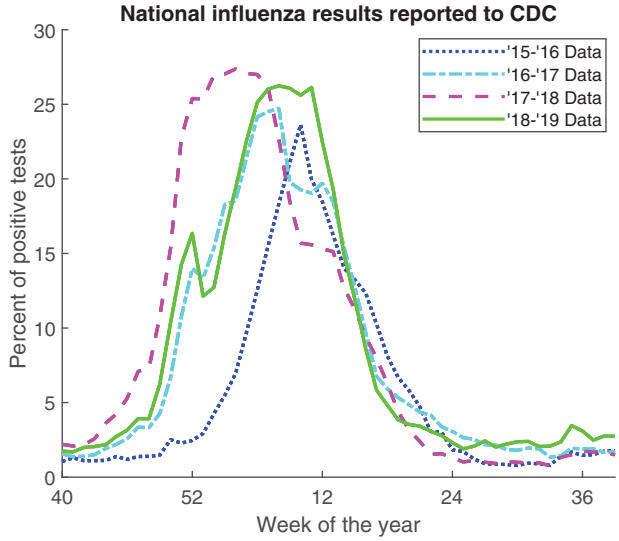

Figure 2. Seasonality of annual incidence of influenza, 2015 to 2019.

Next, we derive the estimated contact rate function at which a susceptible individual becomes infected when contacting an infectious individual. Intuitively, the contact rate determines the instantaneous rate of change to the weekly positivity rate. We propose a novel approach for finding the contact rate by borrowing a fundamental concept from Physics: the contact rate is to the weekly positivity rate as the acceleration is to velocity. That is, if we view the positivity rate in a week as velocity, then the contact rate should be the instantaneous rate of acceleration in the given week. Thus, we take the first derivative of the sine function $f(t)$ with respect to t to find the contact rate as a cosine function:

$$\hat{\beta}(\mathrm{t}) = 1.3764 \cos\left[\frac{2\pi}{43.0102}(\mathrm{t} - 139.2729) + 1\right]. \qquad (7)$$

As such, the contact function Eq. (7) has a maximum at week 2 (in January) and a minimum at week 24 (in June) for a given year, matching the empirical observation that influenza activity often begins in October, peaks sometime between December and February, and lasts as late as May.[3] Note that the constant 1 in Eq. (7) is added to keep the function $\hat{\beta}(\mathrm{t})$ realistic for all integer $\mathrm{t} \in \{1, 2, \ldots, 51, 52\}$. Without the added constant, Eq. (7) oscillates between +1.3764 and −1.3764 over t. If adding any constant <1, then Eq. (7) might render some negative contact rate. If the added constant is >1, then Eq. (7) might render some increasing infection rate for the population even during the summertime.

3.3. Experiment parameters

This study also examines the impact of the length of the infectious period on the size of the epidemic. According to CDC,[3] infected people can be contagious one day before experiencing symptoms, which typically last 3 to 7 days, and can stay contagious for up to 7 days after becoming sick. The contagious period can be longer than 7 days for children and some people with weakened immune systems. Cori et al[28] pointed out that it is impossible to directly observe the duration of the infectious period. The authors reviewed the literature and found that the 95% probability intervals of the mean duration of the infectious period can be any number of days up to 12 days, while the majority of cases having an infectious period are shorter than 2.9 days. Thus, we consider γ, the recovery rate of infected individuals, to vary between $\frac{1}{12}$ and $\frac{1}{2}$. Since it is of interest, we also tracked and observed during our simulations the total number of recovered individuals, as a proxy for the size of the epidemic.

Another uncertainty that we bring into the study is the proportion of people who gain immunity, at least in the beginning of the season. Statistics from the 2018 influenza season showed that, depending on age group, the percentage of people who received an influenza vaccination varies between 30% and 70%, with vaccine effectiveness ranging from 10% to 60%.[29,30] Thus, we let α, the proportion of susceptible individuals fully protected by the vaccine, vary between 3% and 42%. Moreover, we vary I_0, the initial number of infected individuals, between 1 and 100. Lastly, Grohskopf et al[31] pointed out that the observed waning effect might not consistently manifest itself across all age groups, virus subtypes, or seasons. Nonetheless, Ferdinands et al[32] examined the association between influenza vaccine effectiveness and time since vaccination among patients in the United States. The authors found significant evidence that influenza vaccine protection could decline by 6% to 11% per month since the time of vaccination, depending on influenza type. Thus, we vary ζ, the rate at which the number of (newly) vaccinated individuals decreases over time, from 6% to 11%.

3.4. Numerical experiments

We code the system of differential Eqs. (3) to (6) in MATLAB and solve them numerically for the values of a given t under different scenarios (solver *ode45*; www.mathworks.com). When computing, we begin by assigning the initial values of the groups of the population, with N and R_0 being always held constant at 10^6 and at 0, respectively. In addition, every influenza season spans 52 weeks, starting at week 40 of 1 year and ending at week 39 of the following year. During the season, individuals continuously interact with each other, and the size of the four groups changes at the rates defined by the differential equations.

Figure 4 shows the impact of the recovery rate on the number of individuals in the four groups over the course of the influenza season. We observe that an influenza virus that requires a longer recovery time tends to cause the population to experience another uptick in the number of infected individuals at around week 36. We also note that the longer the time the infected individuals take to recover, the larger the epidemic size is—that is, the total number of recovered individuals at the end of the season.

Figure 5 shows that if the population has a larger number of initially infected individuals (I), then the peak of the season would not only arrive sooner but also be smaller. A subtle and counter-intuitive observation is that the epidemic size—that is, the total number of recovered individuals at the end of the season—is actually smaller when I is larger. We will examine this phenomenon in more detail shortly.

Figure 6 shows the impact of the proportion of the vaccinated population on the number of individuals in the four groups over the course of the influenza season. The greater the proportion of individuals receiving the vaccination at the beginning of the season, the smaller the epidemic size (the total number of

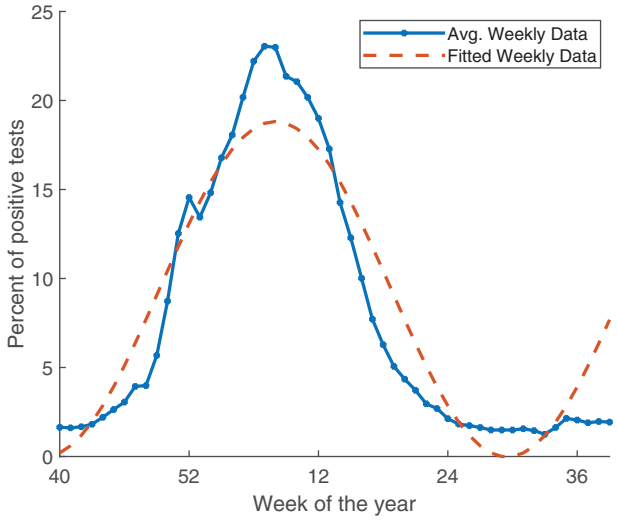

Figure 3. Performance of fitted model vs actual weekly data.

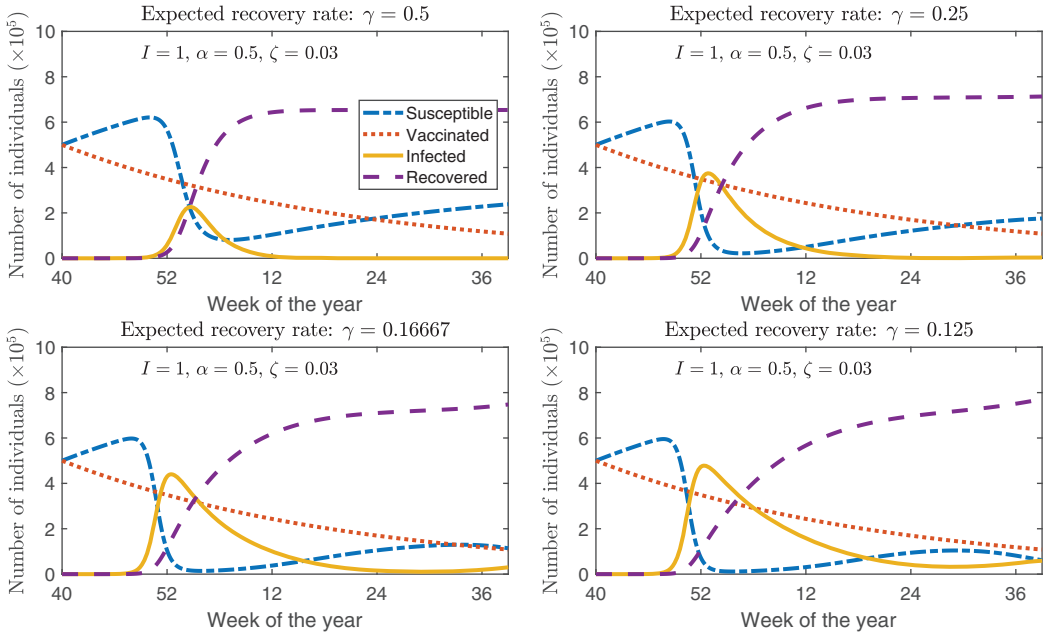

Figure 4. Evolution of the SVIR groups as a function of the recovery rate.

recovered individuals) at the end of the season. An increase in α seems to lead to a decrease in the size of the epidemic, but it also delays the peak of the season, as well as leading to an uptick in infected individuals toward the end of the season.

Figure 7 highlights the missing link in the literature—the effect of the individuals leaking from V to S when the vaccination is subject to the waning effect. Even with a slight increase in the waning effect, for example, ζ from 0 to 6% (i.e., top-left panel to top-right panel), the size of the epidemic could increase by more than 100%. Therefore, researchers studying related topics should not disregard the waning effect. Although a higher waning rate leads to a larger epidemic size, the peak of the season takes place roughly in the same week. The implication is that researchers or practitioners may not be able to tell if the effectiveness of a given vaccine can wane over time by observing the timing of the peak of the season.

Figure 8 shows the epidemic size given four different values for the number of initially infected individuals. Counter-intuitively, relatively faster recovery rates, roughly between 1/12 and 1/7, can actually make the epidemic worse. Another interesting observation is that, for the cases where the recovery rate is greater than about 15%, the greater the number of initially infected individuals, the smaller the epidemic (i.e., the smaller the total number of recovered individuals at the end of the season). Note that for influenza that entails a recovery period of 7 days or fewer, a greater number of initially infected individuals can lead to a decrease in the season's epidemic size. But for influenza that entails a recovery period of 7 days or more, a greater number of initially infected individuals can lead to an increase in the season's epidemic size.

Figure 9 illustrates that the higher the waning rate, the larger the epidemic size. The implication is that the effectiveness of the vaccine must be made as good as possible to effectively mitigate the potential outbreak of an epidemic. Similar to the phenomenon observed in Figure 8, a faster recovery rate might increase the epidemic size, and the phenomenon holds even under different rates of the waning effect.

To conduct a sensitivity analysis, we separately fitted the models using the data of the individual seasons and obtained four different sets of values of the parameters A, B, C, and D as shown

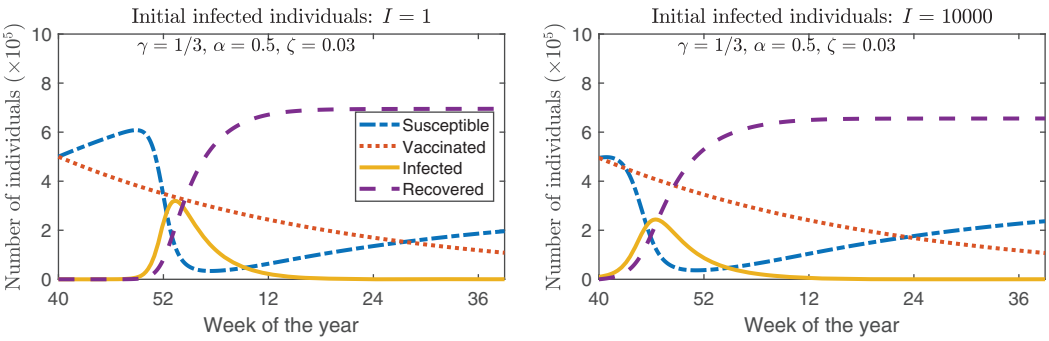

Figure 5. Evolution of the SVIR groups as a function of the size of the initial infected population.

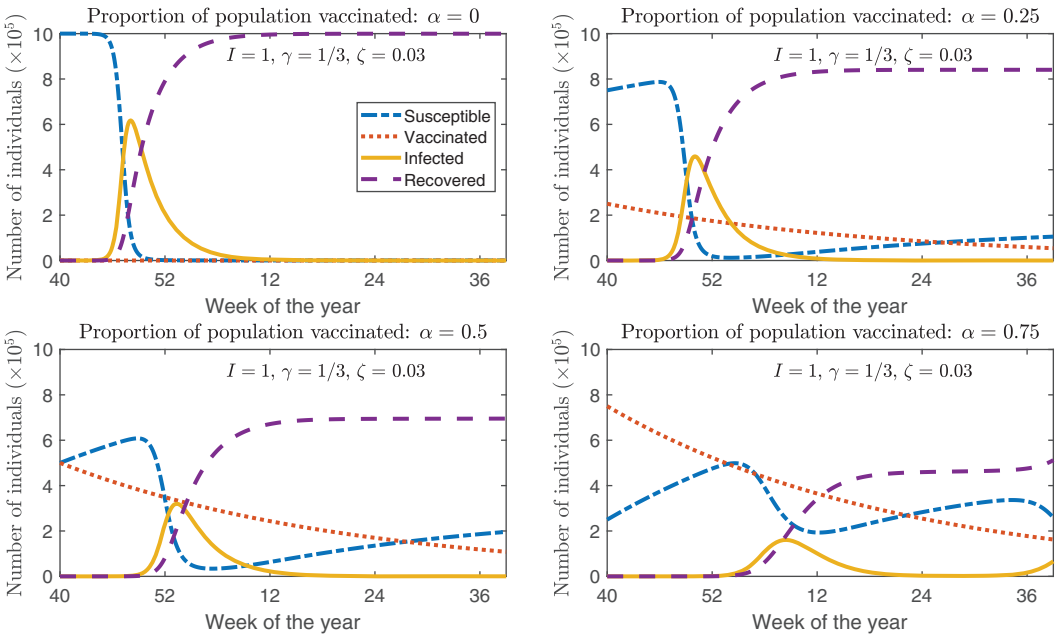

Figure 6. Evolution of the SVIR groups as a function of the proportion of the vaccinated population.

in Table 1. Not reported here, all of the results using the parameter values led to the same conclusions as do those using the average of the four seasons' data.

4. Discussion

Influenza has been a leading cause of death in the United States. Despite vaccination, the number of susceptible, infected, and recovered individuals seems to follow similar patterns year after year.[24] In this study, we combined multiple approaches to better capture the complexities of the influenza epidemic phenomenon. The theoretical contribution of our study lies in fitting empirical influenza data to the models that capture the periodic phenomena of influenza infections and the oscillating contact rate over time. Moreover, we extended the classic SIR model to the SVIR model by incorporating the effect of waning vaccination immunity to better reflect the course and spread of influenza infections. The

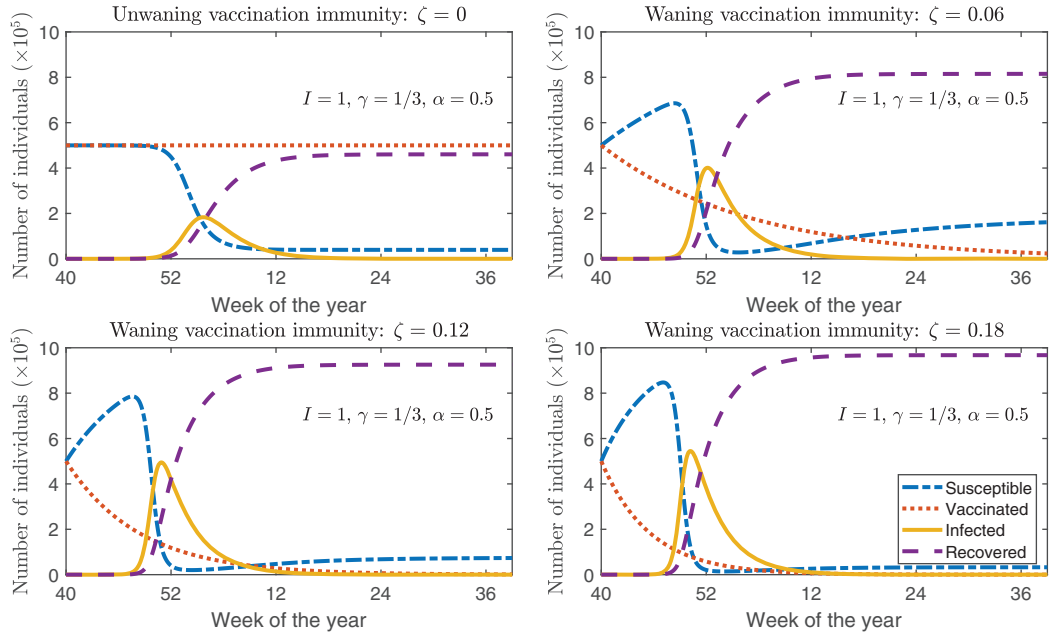

Figure 7. Evolution of the SVIR groups as a function of the unwaning vaccination immunity.

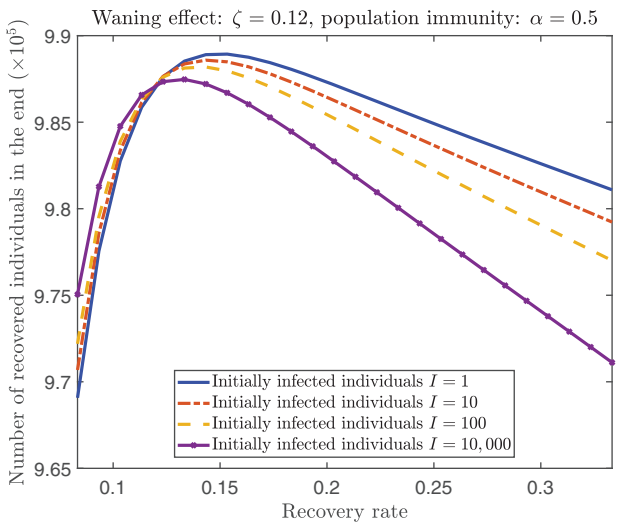

Figure 8. Faster recovery rate does not necessarily reduce the epidemic size, regardless of the number of initially infected individuals.

practical implication of the study lies in simulating the size of the influenza epidemic when varying several model parameters. In particular, we show how an uptick in influenza cases toward the end of the season or even a delay in the peak of the season might be caused by scenarios involving an influenza virus that entails a longer recovery time, or when a greater portion of the population gets vaccinated. The rather counter-intuitive results suggest that a larger number of initially infected individuals might not only bring the influenza season to an end sooner but also reduce the size of the epidemic. Moreover, an influenza virus that entails a faster recovery rate does not necessarily lead to a smaller epidemic size.

One limitation of the study may be attributed to the availability of the less distorted data we chose to use, which was unavailable on the CDC website until 2015. In addition, the differential equation model assumes that all subjects are directly connected

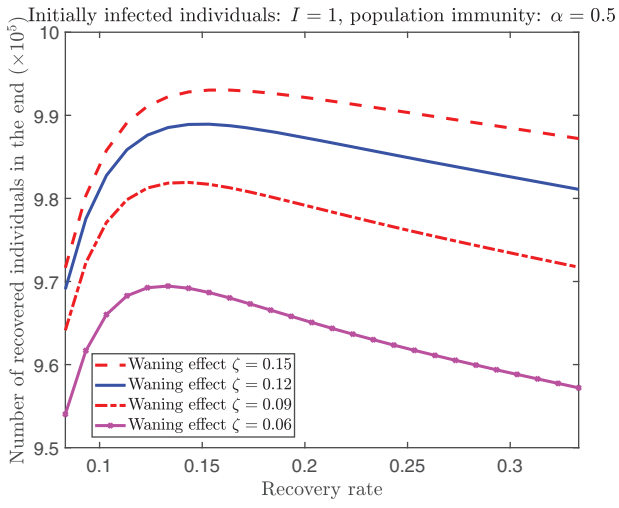

Figure 9. Faster recovery rate does not necessarily reduce the epidemic size, regardless of the rates of the waning effect.

Table 1

Distribution of fitted model parameter values.

Data	'15-'16	'16-'17	'17-'18	'18-'19
A	7.7053	9.5389	10.8499	10.3989
B	37.7859	42.7578	45.6792	42.0445
C	128.3949	138.8957	144.3897	136.6177
D	7.6902	9.5291	10.8344	10.3988

with each other, and as likely to get or spread the disease, which may not be true for populations that are sparsely connected. Nevertheless, the numerical experiments present a number of interesting phenomena that are worth pursuing further.

Future research and extensions of the investigations in this study can consider different types of influenza viruses. According to CDC,[3] both type A and type B influenza viruses are responsible for causing seasonal epidemics of the disease every winter.[10] It has been reported that different types of the influenza virus could show up at different times in an influenza season.[33] Thus, the implications of the waning effect over time we discussed in this study may pan out differently for different types of the influenza virus. Another direction for future research is to consider the group of immunosuppressed individuals in the model.[34] Individuals with immune dysfunction may not respond to the vaccine as well as people without immune dysfunction.[35] Furthermore, people who are severely immunocompromised (e.g., HIV-infected people, organ transplant recipients, or people who undergo immunosuppressive treatments) tend to prolong influenza virus shedding, increase morbidity or mortality following infection, and be reinfected with the same virus strain.[36,37] Thus, researchers can study the impact of immunosuppression on the SVIR model. Finally, researchers may consider applying the framework of this study and analyze influenza data from other countries or regions, for additional insights.

As the entire world is increasingly inoculated with COVID-19 vaccines, we anticipate that many more studies will be underway to further model the immunity provided by the vaccines. The waning effect we consider in this article, even though introduced in the context of an influenza epidemic, could become especially relevant in modeling and understanding the COVID-19 pandemic immunity-related parameters. At the same time, the reliability and the frequency of data reporting will have a direct effect on gaining a better understanding of vaccine administration.

Author contributions

Conceptualization: Chun-Miin (Jimmy) Chen, Alia C. Stanciu.
Data curation: Chun-Miin (Jimmy) Chen.
Formal analysis: Chun-Miin (Jimmy) Chen, Alia C. Stanciu.
Funding acquisition: Chun-Miin (Jimmy) Chen.
Investigation: Chun-Miin (Jimmy) Chen, Alia C. Stanciu.
Methodology: Chun-Miin (Jimmy) Chen, Alia C. Stanciu.
Project administration: Chun-Miin (Jimmy) Chen, Alia C. Stanciu.
Resources: Chun-Miin (Jimmy) Chen.
Software: Chun-Miin (Jimmy) Chen.
Supervision: Chun-Miin (Jimmy) Chen.
Validation: Chun-Miin (Jimmy) Chen, Alia C. Stanciu.
Visualization: Chun-Miin (Jimmy) Chen.

Writing – original draft: Chun-Miin (Jimmy) Chen, Alia C. Stanciu.
Writing – review & editing: Chun-Miin (Jimmy) Chen, Alia C. Stanciu.

References

[1] Kochanek KD, Murphy SL, Xu J, Arias E. Deaths: Final Data for 2017. Natl Vital Stat Rep 2019;68:1–77.
[2] World Health Organuization. Ask the expert: Influenza Q&A. 2018. Available at: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal). Accessed September 18, 2020.
[3] Centers for Disease Control and Prevention. Influenza (Flu). 2019. Available at: https://www.cdc.gov/flu/. Accessed September 18, 2020.
[4] Schroeder K. Global challenges in seasonal influenza vaccine supply, use, and policy. Intersect Stanford J Sci Technol Soc 2018;12:1–23.
[5] World Health Organization. Influenza vaccine response during the start of a pandemic: report of the Third WHO informal consultation. 2019. Available at: https://apps.who.int/iris/bitstream/handle/10665/325973/WHO-WHE-IHM-2019.5-eng.pdf. Accessed September 18, 2020.
[6] Smith DJ, Lapedes AS, de Jong JC, et al. Mapping the antigenic and genetic evolution of influenza virus. Science 2004;305:371–6.
[7] Kissling E, Valenciano M, Larrauri A, et al. Low and decreasing vaccine effectiveness against influenza A(H3) in 2011/12 among vaccination target groups in Europe: results from the I-MOVE multicentre case-control study. Eurosurveillance 2013;18:20390.
[8] Pebody RG, Andrews N, McMenamin J, et al. Vaccine effectiveness of 2011/12 trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: evidence of waning intra-seasonal protection. Eurosurveillance 2013;18:20389.
[9] Belongia EA, Sundaram ME, McClure DL, Meece JK, Ferdinands J, VanWormer JJ. Waning vaccine protection against influenza A (H3N2) illness in children and older adults during a single season. Vaccine 2015;33:246–51.
[10] Hill EM, Petrou S, De Lusignan S, Yonova I, Keeling MJ. Seasonal influenza: modelling approaches to capture immunity propagation. PLoS Comput Biol 2019;15:1–26.
[11] Andradóttir S, Chiu W, Goldsman D, et al. Simulation of strategies for containing pandemic influenza. In Proceedings of the 2010 Winter Simulation Conference: Baltimore, Maryland; 2010, pp. 2221–9.
[12] Paleshi A, Evans GW, Heragu SS, Moghaddam KS. Simulation of mitigation strategies for a pandemic influenza. In Proceedings of the 2011 Winter Simulation Conference: Phoenix, Arizona; 2011, pp. 1340–8.
[13] Goeyvaerts N, Willem L, Van Kerckhove K, et al. Estimating dynamic transmission model parameters for seasonal influenza by fitting to age and season-specific influenza-like illness incidence. Epidemics 2015;13:1–9.
[14] Weidemann F, Remschmidt C, Buda S, Buchholz U, Ultsch B, Wichmann O. Is the impact of childhood influenza vaccination less than expected: a transmission modelling study. BMC Infect Dis 2017;17:258–72.
[15] Finkenstädt BF, Morton A, Rand DA. Modelling antigenic drift in weekly flu incidence. Stat Med 2005;24:3447–61.
[16] Dushoff J, Plotkin JB, Viboud C, Earn DJ, Simonsen L. Mortality due to influenza in the United States—an annualized regression approach using multiple-cause mortality data. Am J Epidemiol 2006;163:181–7.
[17] Schanzer DL, Sevenhuysen C, Winchester B, Mersereau T. Estimating influenza deaths in Canada, 1992–2009. PLoS One 2013;8:11–1.
[18] Towers S, Geisse KV, Zheng Y, Feng Z. Antiviral treatment for pandemic influenza: assessing potential repercussions using a seasonally forced SIR model. J Theor Biol 2011;289:259–68.
[19] Towers S, Feng Z. Pandemic H1N1 influenza: predicting the course of a pandemic and assessing the efficacy of the planned vaccination programme in the United States. Eurosurveillance 2009;14:19358.
[20] Dushoff J, Plotkin JB, Levin SA, Earn DJ. Dynamical resonance can account for seasonality of influenza epidemics. Proc Natl Acad Sci 2004;101:16915–6.
[21] Kermack WO, McKendrick AG. A contribution to the mathematical theory of epidemics. Proceedings of the Royal Society of London Series A, Containing Papers of a Mathematical and Physical Character; 1927, vol. 115, pp. 700–21.
[22] Aleman DM, Wibisono TG, Schwartz B. Accounting for individual behaviors in a pandemic disease spread model. In Proceedings of the 2009 Winter Simulation Conference: Austin, Texas; 2009, pp. 1977–85.
[23] Heffernan JM, Keeling MJ. Implications of vaccination and waning immunity. Proc R Soc B Biol Sci 2009;276:2071–80.
[24] Martinez-Moyano IJ, Macal CM. A primer for hybrid modeling and simulation. In Proceedings of the 2016 Winter Simulation Conference: Arlington, Virginia; 2016, pp. 133–47.
[25] Feng Z, Towers S, Yang Y. Modeling the effects of vaccination and treatment on pandemic influenza. AAPS J 2011;13:427–37.
[26] Yang J, Zhang J, Han T, et al. Effectiveness, immunogenicity, and safety of influenza vaccines with MF59 adjuvant in healthy people of different age groups: a systematic review and meta-analysis. Medicine 2020;99:
[27] Rappuoli R, Del Giudice G. Influenza Vaccines for the Future. London, UK: Springer Basel; 2011;274 p.
[28] Cori A, Valleron AJ, Carrat F, Tomba GS, Thomas G, Boëlle PY. Estimating influenza latency and infectious period durations using viral excretion data. Epidemics 2012;4:132–8.
[29] Centers for Disease Control and Prevention. National Center for Health Statistic. 2015. Available at: https://www.cdc.gov/nchs/fastats/flu.htm. Accessed September 18, 2020.
[30] McGinty JC. *Effectiveness of Flu Shot Is 60%–in a Good Year*. 2017. Available at: https://www.wsj.com/articles/effectiveness-of-flu-shot-is-60-in-a-good-year-1512741601. Accessed September 18, 2020.
[31] Grohskopf LA, Alyanak E, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2019-20 influenza season. MMWR Recommend Rep 2019;68:1.
[32] Ferdinands JM, Fry AM, Reynolds S, et al. Intraseason waning of influenza vaccine protection: evidence from the US influenza vaccine effectiveness network, 2011–2012 through 2014–2015. Clin Infect Dis 2017;64:544–50.
[33] Rettner R. *This year's flu shot doesn't match what's circulating. Here's what that means*. 2020. Available at: https://www.livescience.com/flu-shot-bad-match-influenza-b.html. Accessed September 18, 2020.
[34] Harpaz R, Dahl RM, Dooling KL. Prevalence of immunosuppression among US Adults, 2013. JAMA 2016;316:2547–8.
[35] Kunisaki KM, Janoff EN. Influenza in immunosuppressed populations: a review of infection frequency, morbidity, mortality, and vaccine responses. Lancet Infect Dis 2009;9:493–504.
[36] Memoli MJ, Athota R, Reed S, et al. The natural history of influenza infection in the severely immunocompromised vs nonimmunocompromised hosts. Clin Infect Dis 2014;58:214–24.
[37] Pelletier G, Déry P, Abed Y, Boivin G. Respiratory tract reinfections by the new human Metapneumovirus in an immunocompromised child. Emerg Infect Dis 2002;8:976–8.